VOLUME 59 NUMBER 1

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JULY 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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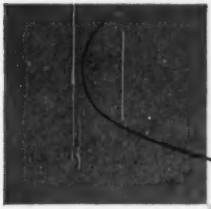

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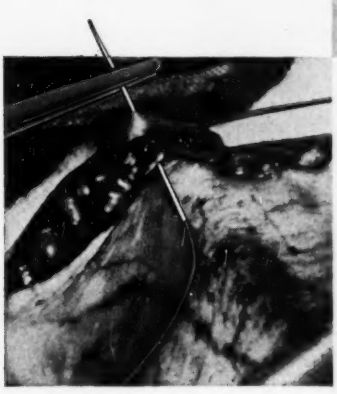

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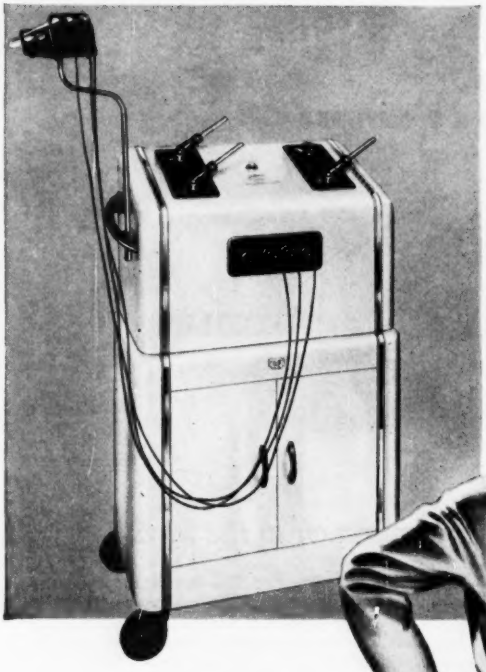

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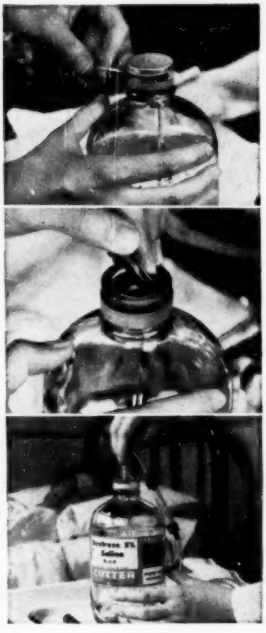

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VOLUME 59 JULY 1949 NUMBER 1

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CONGENITAL CYSTIC DISEASE OF THE LUNG IN INFANTS AND IN CHILDREN

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AND

JANET B. HARDY, M.D.

BALTIMORE

DESPITE a rapidly growing literature on cysts of the lung, there still exists a considerable disparity of opinion with reference to their genesis, diagnosis and mode of treatment. A recent monograph [1] stated:

> Congenital cystic disease: Anatomic studies indicate that this is an extremely rare condition. It has not been found at necropsy at The Babies Hospital during a period of fifty years. Schenck quotes Lederer as having failed to find a single instance of congenital cystic disease in five thousand necropsies. It is now evident that many cases which have suggested congenital cysts roentgenographically were probably examples of acquired emphysematous cavities caused by check-valvular bronchial obstruction.

The present cases of cystic disease of the lung in infants and children exemplify most types of cystic disease of the lung seen and present a fair sample of the types of accompanying anatomic anomalies (fig. 1). Ten of the 12 patients have been seen consecutively in the past five years, 8 of them within the past year.

The occurrence of the disease in newborn infants (Flemming Möller [2]) establishes it as congenital. The embryologic mechanism and the time of formation of the defect have not been established. The frequent association of anomalous lobar segments—as in cases 7 and 8 and as reported by Harrington,[3] Flemming Möller [2] and others—suggests a gross developmental disturbance, as does the frequent occurrence of anomalous systemic arteries supplying the lung (cases 8 and 9 and reports by Douglass,[4] Haight [5] and others). The occurrence in

From the Department of Surgery of The Johns Hopkins Medical School and Hospital and the Harriet Lane Home.

1. Caffee, J.: Pediatric X-Ray Diagnosis, Chicago, The Year Book Publishers, Inc., 1945, p. 234.

2. Flemming Möller, P.: Congenital Thoracic Cysts and Lung Deformities in the Roentgen Picture, Acta. radiol. **9**:460, 1928.

3. Harrington, S. W.: Surgical Treatment of Intrathoracic Tumors, Arch. Surg. **19**:1679 (Dec.) 1929.

4. Douglass, R., in discussion on Brown and Brock.[13]

5. Haight, C., in discussion on Brown and Brock.[13]

the same lobes of adenomatous growth of the mucous glands, as seen in case 6 (fig. 14*A*), has been reported by others. These various anomalies are usually not accompanied with major defects in other organs. Supplementary lobes and anomalous vessels are found without cysts of the lung and cannot in themselves be causative factors. Lobes supplied by anomalous arteries may also have normal pulmonary arteries. It is of interest that in a series of over 400 cases of pulmonic stenosis observed at the Johns Hopkins Hospital, in some of which the pulmonary arteries to one or both lungs were absent, only 1 patient has been found to have what appears to be a cyst of the lung.

Abnormally situated vessels present a hazard during the course of operation which may be minimized by an awareness of their possible

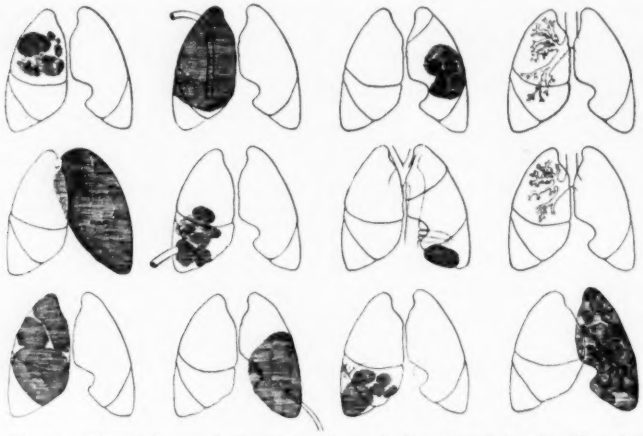

Fig. 1.—Distribution and character of the lesions found in the 12 patients reported on. First column, cases 1, 2 and 3; second column, cases 4, 5 and 6; third column, cases 7, 8 and 9; fourth column, cases 10, 11 and 12. The patients in cases 1, 2 and 3 were infants; those in 2 and 6 had a check valve mechanism; those in 4, 5 and 6 had been drained for empyema, and were admitted with tubes in place; those in 7 and 8 had trilobed left lungs; those in 8 and 9 had anomalous systemic arteries supplying the affected lobes; those in 10 and 11 had a cystic bronchiectasis of the right upper lobe, and the patient in case 12 had a left lung honeycombed with cysts.

presence. McCotter in 1910 [6] analyzed 9 cases of anomalous pulmonary arterial blood supply gathered from the literature of the preceding century. In 5 instances these arteries supplied accessory lower lobes of the infracardiac type, four of which were situated on the left and the fifth on the right. These vessels all arose from the aorta between

6. McCotter, R. E.: On the Occurrence of Pulmonary Arteries Arising from the Aorta, Anat. Rec. **4**:291, 1910.

the levels of the seventh and tenth thoracic vertebrae. In the remaining 4 cases the anomalous vessels were not associated with accessory lobes but represented an abnormal blood supply to lobes which seemed otherwise normal. .In 3 of these the vessels arose from the thoracic aorta; two supplied the lower lobe on the left, and the third supplied the lower lobe on the right. In the fourth the vessel arose from the abdominal aorta, and after passing through the esophageal hiatus in the diaphragm it branched to supply the lower lobes of both right and left lungs.

Batts [7] described a patient in whom a large artery arising from the celiac plexus passed through the diaphragm to supply the lower lobe of the left lung. In Harris' [8] case an operative fatality resulted from hemorrhage due to the inadvertent cutting of a large artery arising from the thoracic aorta 2 cm. above the diaphragm and entering the lower lobe of the left lung posteriorly at the level of the free margin of the pulmonary ligament.

In discussing Moersch and Clagett's report on pulmonary cysts, Head [9] described a cystic accessory pulmonary lobe which had a bronchial system continuous with that of the normal lower lobe of the left lung but which derived its main blood supply from the thoracic aorta. In further discussion Butler [10] commented on finding anomalous systemic arteries to the lung in at least four operations for congenital cystic disease, with fatal hemorrhage from such a vessel in 1 instance.

As Harris and Ivor [8] have pointed out, the anomalous pulmonary arteries fall into two groups, both consisting of persistent enlargement of the embryonic capillary plexuses. In the first group the connections are between the pulmonary artery and the subclavian, the superior intercostal or the ventral splanchnic branches of the aorta. In the second group the connections are between the pulmonary artery and the celiac axis.

Various authors have commented on the association between accessory pulmonary lobar segments and cystic disease. Schenck [11] in his analysis of the 232 cases of cystic disease reported up to 1936 pointed out that 38 of the patients were found at autopsy to have other malformations in addition to the cystic disease of the lung. The most

7. Batts, M.: A Pulmonary Artery Arising from the Aorta, J. Thoracic Surg. **8**:565, 1939.

8. Harris, H. A., and Ivor, L.: Anomalies of the Lung with Special Reference to Danger of Abnormal Vessels in Lobectomy, J. Thoracic Surg. **9**:666, 1940.

9. Head, J., in discussion on Moersch.[14]

10. Butler, E. F., in discussion on Moersch.[14]

11. Schenck, S. G.: Congenital Cystic Disease of the Lungs, Am. J. Roentgenol. **35**:608, 1936.

frequent of these congenital abnormalities was the presence of an accessory pulmonary lobe harboring the cystic areas. This was found in 17 patients.

The derivation of these cysts from malformed bronchi is clearly indicated by the unquestionably bronchial character of the epithelium (figs. 4 *B* and 12 *B*) and the elastic tissue, smooth muscle or cartilage in the walls. Again, the cysts are almost invariably at the periphery of the lung (unless the lung is entirely honeycombed, as in case 12, fig. 25), which suggests that it is the small peripheral bronchi which have failed to establish communication with the air spaces.

CLINICAL CHARACTERISTICS

The clinical behavior of cysts of the lung can be predicted from their structure and the known mechanism of the symptomatology of pulmonary disease. The division of congenital cysts into "air cysts" and "fluid cysts" is probably arbitrary although it suggests at once the salient characteristic of the given cyst or cysts. In every one of our patients communication of the cyst or cysts with the bronchial tree was demonstrated in one or several ways. In cases 6, 7, 10, 11 and 12 bronchograms showed lipiodol® (iodized poppyseed oil 40 per cent) in the cysts. At operation in cases 2 and 6 a check valve communication with a large bronchus was demonstrated. The patients in cases 4, 5 and 6, who were treated elsewhere for what was thought to be empyema, had frank bronchopleural fistulas, intermittent in cases 4 and 5 and constant in case 6. In case 8 anthracotic pigment in the cyst and copious purulent sputum proved the bronchial communication. In the others, cases 1, 3 and 9, air in the cysts was visible in the roentgenograms. Demonstration of a bronchial communication in the gross specimen has been notoriously difficult even when bronchography has proved such communication to exist. The presence in the lung of a cavity lined by secreting epithelium and communicating with the bronchial tree gives rise to cough, expectoration, infection of the cyst and a train of consequences similar to those seen in cases of bronchiectasis and of pulmonary abscess. The infection originating in these cysts may give rise to a secondary bronchiectasis as a result of compression of neighboring pulmonary tissue and overflow of purulent secretions. The mucous membrane lining these cysts is usually intact, and, as might be expected, none of the patients had hemoptysis or metastatic abscesses.

In only 1 case (case 6) was the cyst found on a routine roentgenogram of an asymptomatic child. This child subsequently had frequent attacks of "bronchopneumonia" and finally had a cyst drained six years before we saw him. Seven of the others had a chronic cough,

the age at onset being from 3 weeks to 5 years. In 3 who were previously asymptomatic evidence of acute pulmonary infection developed at the ages of 8, 9 and 12 years. Six of the patients had repeated bouts of pulmonary infection severe enough to be called pneumonia. Dyspnea, constant or in episodes, was observed in all patients. Severe cyanosis was seen only in the patient in case 10, who had associated bronchiectasis of the lower lobes.

Inevitability of infection in cysts of the lungs is the strongest reason for early, prophylactic operation. The advisability of operation is frequently questioned in children with apparently asymptomatic cysts, as in the patient in case 1, who, at the age of 3 months, had had a cough for three weeks and was found to have cysts in the right upper pulmonary field. He was well nourished, afebrile and vigorous. Operation was advised and performed to forestall the inevitable infection. Aspiration of the cysts at operation showed yellow fluid which yielded a pure culture of staphylococci. The microscopic sections (fig. 4) showed extensive inflammation of the lining of the cyst despite the age of the patient and absence of symptoms. In only 1 patient (case 2, fig. 7) was there absence of considerable inflammatory changes in the cyst. The single death in the series, in case 3, was due to pneumonia supervening in a child with heavily infected cysts who had unfortunately been sent home "to be built up" (fig. 8).

Rupture of cysts, with resultant pneumothorax or empyema or both, has been reported but was not seen in this series. Similarly, others have reported hemoptysis in patients with cyst of the lung. One would expect hemoptysis only if the infection has been severe enough to destroy the cyst lining or if there is associated bronchiectasis.

The literature is replete with reports of patients with cystic disease of the lung erroneously treated for empyema (Maier & Haight [12]), the true source of the infected fluid being discovered subsequently. The patients in cases 4, 5 and 6 (figs. 9 to 14) all came to us with a drainage tube in place. It has frequently been remarked that long-continued drainage of cysts of the lungs does not affect their size—which is borne out by the roentgenograms of these patients seven months, five years and six years, respectively, after drainage was instituted.

One occasionally sees tension cysts, the so-called giant cysts or gas cysts, with symptoms due chiefly to pressure. Cases 2 and 6 exemplify the mechanism in such instances. In the first, involving a year old infant, the entire left side of the chest was filled with a huge air-containing cyst (fig. 5) which crossed the midline to the right. At operation

12. Maier, H. C., and Haight, C.: Large Infected Solitary Pulmonary Cysts Simulating Empyema, J. Thoracic Surg. **9**:471, 1940.

the cyst was so large (fig. 6) that it was aspirated with a needle and emptied of air to facilitate the operation. Almost at once it refilled with air and became as large and tense as ever. It seemed clear that there was a one way valve which permitted ingress of air until the tension within the cyst was sufficient to occlude the bronchus, equilibrium being established at a point within the range of tolerance of the patient. To complete the operation it was necessary to leave a large needle penetrating the cyst cavity, permitting release of the entrapped air. In the second instance (case 6) there was a cutaneous fistula of six years' duration which had given the patient no difficulty except for the slight annoyance incident to a cutaneous bronchial fistula. When, at operation, this sinus tract was dissected out within the chest and clamped off, the cyst began to balloon out tensely. As soon as the clamp was released the cyst returned to its former size. Again there was a one way valve, which in this case had been compensated for by a permanent external fistula.

While the general systemic response has varied with the extent of the pulmonary tissue involved and the degree of infection in it, clubbing of the fingers appears to be singularly infrequent, occurring in only 2 of our cases, 10 and 12.

PATHOLOGIC CHARACTERISTICS

The ultimate criterion for the diagnosis of congenital cystic disease of the lung in most cases is the gross and microscopic pathologic picture. It is remarkable how little the characteristics of congenital cysts are altered by prolonged and severe infection. In our present series we recognize three types of cysts on gross pathologic grounds and only two on microscopic grounds. Cases 3, 9 and 12 represent lobes or lungs honeycombed by cysts, most graphically seen in case 12, in which the entire left lung was replaced by innumerable cysts of varying size (fig. 25). In case 9 the lower lobe of the right lung (fig. 19) and in case 3 the upper lobe (fig. 8) were similarly affected. It occasionally occurs that all lobes of both lungs are so diseased, and in July 1945 one of us (M. M. R.) saw a patient in whom this occurred in the wards of the Brompton Hospital in London on the service of A. Tudor-Edwards—a 6 year old girl with both lungs presenting the appearance of the left lung in our case 12. The patients in cases 1, 2, 4, 5, 6 and 8 had cysts of one lobe and the patient in case 7 had cysts of two lobes, the cysts being either unilocular or else a few large cysts coalescing to form what was essentially a unilocular cyst with outpouchings. Microscopically the cysts in both these types are indistinguishable. Characteristically the lining is of tall, columnar, typical bronchial epithelium. Cilia can be plainly seen in the photomicrographs in cases 1, 5 and 8, despite the fact that the patient in case 5

had had a rib resection and had worn a drainage tube for five years and the patient in case 8 had a cyst filled with pus and had had the clinical symptoms of a pulmonary abscess. Case 2 fits most closely the group of so-called air cysts, and here the epithelium is low cuboidal. In the cysts in case 3 gross infection has left only granulation tissue, with occasional epithelial remnants which are low cuboidal. The structure of the cyst walls varies. Some photomicrographs show well defined layers of smooth muscle and elastic tissue; in others there is only a nondescript, laminated fibrous wall. Many of the cysts have bronchial glands in their wall or beneath. Figure 14 *A* from case 6 shows an adenomatous proliferation of mucous glands deriving from the cyst epithelium, and figure 14 *B* from the same case shows a similar proliferation of mucous glands in the parenchyma of the lung at a distance from the cyst wall. The lungs have usually been scarred and compressed near the cysts. It is remarkable that in the gross specimen the lining of the cyst usually seems white, shiny and smooth regardless of the amount of inflammation which may appear. The trabeculation of the walls of many of the cysts produces an appearance of involved infolding in the microscopic section.

Our cases 10 and 11 present the third type of cyst, based on the gross appearance. These are perhaps the last cases left in the group of "congenital bronchiectasis," a once popular diagnosis. The history of the patients as given here, the peculiar site of the disease—the upper lobe of the right lung—and the unusual arrangement of the uniform sacculations along the bronchial tree all suggest a congenital malformation of the bronchi. On the basis of the microscopic picture it is not possible to make a categoric differentiation from acquired bronchiectasis. However, the photomicrographs of case 10 show a large bronchial structure with well preserved mucosa, a thick fibrous wall, astonishingly little evidence of infection and no cartilage at all. Beneath the wall of the large cavity is a cross section of what appears to be a smaller cyst. In case 11 also the photomicrographs show a curious lack of inflammation. There is dense scarring of the lung, with numerous large bronchus-like tubes. The epithelium is well preserved. In some areas are many small, round, epithelium-lined spaces, probably regenerated alveoli but possibly small cystic spaces. The preponderant evidence in these 2 cases is in favor of something other than ordinary bronchiectasis, and we feel justified in suggesting that they may represent instances of congenital diffuse saccular dilatation of the bronchi in the upper lobe of the right lung, a special variety of cystic disease. The concept of "congenital bronchiectasis" has deservedly lost its popularity as a consequence of greater familiarity with pulmonary disease in children. Bronchiectasis is in large part a disease of childhood, at least one originating during childhood, but congenital dilatation of the

bronchi is an uncommon condition rather than one frequently met, as used to be thought. The picture presented by cases 10 and 11 has not been seen in a considerable number of children with bronchiectasis.

Dr. Richard H. Follis Jr., of the Department of Pathology, has reviewed the pathologic material with us.

DIAGNOSIS

The diagnosis is based largely on the roentgenographic appearance of the lesions and has usually been fairly obvious. It was in doubt only in case 8, in which a pulmonary abscess was considered to be present until, at operation, the finding of anomalous arteries and a trilobed left lung suggested the probability that this was a cyst of the lung. The photomicrographs (fig. 18 *B*) unquestionably show a cyst. In reviewing the records of the Harriet Lane Home, we were struck by the fact that whenever there was real difficulty in making a categoric diagnosis of cystic disease it was ultimately determined that some other condition obtained. In infants and children pulmonary abscesses and spontaneous pneumothoraces or pyopneumothoraces have given rise to the most diagnostic confusion. Abscesses usually have more surrounding inflammatory reaction in the pulmonary parenchyma, and there is an acute onset of symptoms following a respiratory infection. In children abscesses usually resolve but occasionally cause empyema. In spontaneous pneumothorax there is usually not the clearly outlined spherical air pocket seen in cystic disease. Obviously, if pneumothorax is a likely diagnostic possibility, operation should be deferred to permit time for the resorption of air to make the diagnosis clear. Occasionally this may take months. In children, bronchiectasis has not suggested cystic disease of the lung. Tuberculous cavities may be embarrassingly like cysts both in children and in adults. Eventually one will undoubtedly encounter a case of cystic disease with superimposed tuberculosis, but it would appear sound to reckon as tuberculous any cystic cavity in a patient whose sputum contains the organisms of the disease.

TREATMENT

The treatment of cystic disease of the lung is now on a sound basis. An ill drained cyst communicating with a bronchus presents the constant hazard of infection. The problem is a mechanical one. Drugs, bronchoscopic aspiration and other forms of treatment offer only palliation. Drainage of the cyst, if it is unilocular and drainage is dependent as in case 6, produces relief from all symptoms and establishes a bronchopleural fistula. It has been recommended (Brown and Brock[13]) that

13. Brown, H. L., and Brock, W.: A Method of Treatment of Large Pulmonary Air Cysts (Balloon Cysts) by an Endocutaneous Flap, J. Thoracic Surg. **11**:617, 1942.

permanent fistulas be created by suturing the skin into the cysts. Such methods are still palliative and may not be successful. The proper treatment seems to be extirpation of the cyst or cysts. Usually this requires a lobectomy, but it may be possible to remove the cyst wall without any pulmonary parenchyma. Cauterization of the cyst wall and attempted closure of the bronchial fistulas are, again, attempts at less direct relief of the patient's difficulty. It has been suggested that infected cysts be first drained and then resected (Maier [12]). We feel that this only complicates the ultimate operation. Preoperative therapy should consist in postural drainage, repeated bronchoscopic aspiration and the administration of penicillin aerosol and penicillin intramuscularly. Ten of the 12 patients were subjected to a lobectomy and 1 to a pneumonectomy, and all 11 recovered without the occurrence of empyema or fistula, although several patients previously had been febrile and had thick pus in their cysts. One patient (case 3) was sent home at the age of 8 months for improvement of her condition before operation and died within three weeks of an acute recrudescence of her pulmonary infection.

The time for operation is the time at which the diagnosis is made. In the absence of complicating factors, children with congenital cystic disease of the lung should be operated on whether the cysts are symptomatic or not. Infection is an almost invariable occurrence if the cysts are not removed. Reports by Moersch [14] and Graham [15] suggest that carcinoma may develop within a cyst. Infants stand pulmonary surgery remarkably well, and the procedures are actually much easier than in adults. The patient in case 1 was only 3 months old, and Gross [16] has reported a pneumonectomy in a 3 week old infant.[16a] We feel that in a case of uncomplicated unilateral cystic disease one is not justified in postponing operation "until the child grows larger." In operating it is important to remember the frequent occurrence of anomalies of lobes and vessels. In our case 7, with three lobes on the left, the "upper lobe" (actually the apical and subapical segments of the upper lobe) was a minute segment of pulmonary tissue, completely collapsed against the inner corner of the dome of the pleura. This lobe was not removed and has since filled the entire left pleural cavity (fig. 15 *D*). The anomalous systemic vessels in cases 8 and 9 were readily seen and gave rise to no technical difficulty.

14. Moersch, H. J., and Clagett, O. T.: Pulmonary Cysts, J. Thoracic Surg. **16**:179, 1947.

15. Graham, E., in discussion on Moersch.[14]

16. Gross, R.: Congenital Cystic Lung: Successful Pneumonectomy in a Three Weeks Old Baby, Ann. Surg. **123**:229, 1946.

16a. Since this paper was submitted, Burnett and Caswell have reported the successful outcome of lobectomy on an even younger patient for severe respiratory distress (Burnett, W. E., and Caswell, H. T.: Lobectomy for Pulmonary Cysts in a Fifteen-Day Old Infant with Recovery, Surgery **23**:84-91, 1948).

REPORT OF CASES

CASE 1.—E. M., a white male infant, was 13 weeks of age at operation. He had a hacking cough for three weeks before his admission to the hospital. A roentgenogram taken to investigate the cough showed a mass in the right upper region of the chest. Two roentgen treatments produced no change, and he was referred to the hospital.

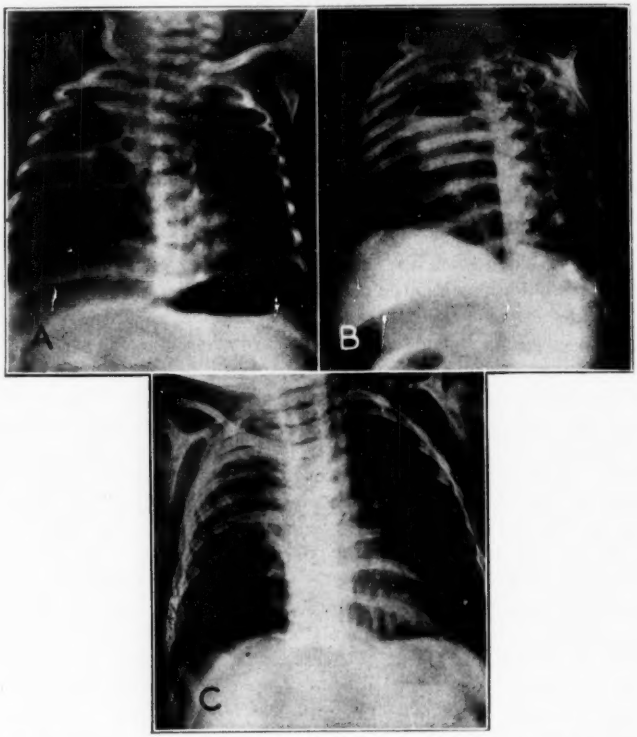

Fig. 2 (case 1).—*A* and *B*, roentgenograms, anteroposterior and oblique views, showing cysts in right upper pulmonary field. *C*, postoperative roentgenogram showing residual pleural thickening.

Physical examination showed a vigorous, healthy-looking infant. There was no asymmetry of the chest. The percussion note was impaired over the right upper region of the chest anteriorly and posteriorly, and in this area there were no breath sounds. Roentgenograms showed what was interpreted as a cystic tumor of the upper lobe of the right lung, thought to be multilocular (fig. 2). Air was seen in several round cystic spaces in a diffusely opaque upper lobe. There was a good deal of discussion on the advisability of operation since the child

seemed so well and had no fever and only a slight cough. Operation was advised because of the strong probability that infection would supervene in what were thought to be congenital cysts.

Operation (March 2, 1943, Dr. Blalock; upper and middle lobes of right lung excised).—The upper lobe alone seemed involved, but it was fused to the middle lobe, which was removed with it. One of the cysts tore and leaked a little yellow fluid, which on culture yielded Staphylococcus albus. After operation the child's course was uneventful except for slow reexpansion of the lung.

Pathologic Report.—The specimen (fig. 3) consists of the upper and middle lobes of the right lung of an infant. The upper lobe is largely occupied by a multilocular cyst 5.5 cm. in greatest diameter. The cyst is seen to be filled with pus. The lining, for the most part well preserved, consists of tall, columnar ciliated bronchial epithelium (fig. 4). There are a few mucous glands in the wall of the cyst and a narrow layer of smooth muscle between the basement membrane and the fibrous wall of the cyst. The cyst wall shows acute inflammation (fig. 4*A*), and the underlying lung shows inflammation and organization, with obliteration of

Fig. 3 (case 1).—Gross specimen. The cyst is collapsed, but the communicating cavities are seen.

alveoli and relative isolation of bronchi. Eosinophils are profusely distributed in the inflamed lining. The inflammation seems of greater duration than the clinical history would indicate.

The child has been asymptomatic since. On March 1, 1947, when last seen, he was well and his lungs were clear on physical and roentgenographic examination.

Summary.—A 13 week old child underwent excision of the upper and middle lobes of the right lung for multilocular cysts of the upper lobe. Despite absence of fever or signs of respiratory infection and despite the brief history, the cyst was infected and there were extensive inflammatory changes. The child has been well ever since.

CASE 2.—V. W., a white male infant, was 12 months of age at the time of operation. He had always eaten poorly and had gained little weight. From the time he was 5 months old be suffered one mild respiratory attack after another. He was hospitalized for two and a half months, being discharged when he was 10 months old. Shortly thereafter he had a severe respiratory infection called bronchitis. Since then he had gone progressively downhill.

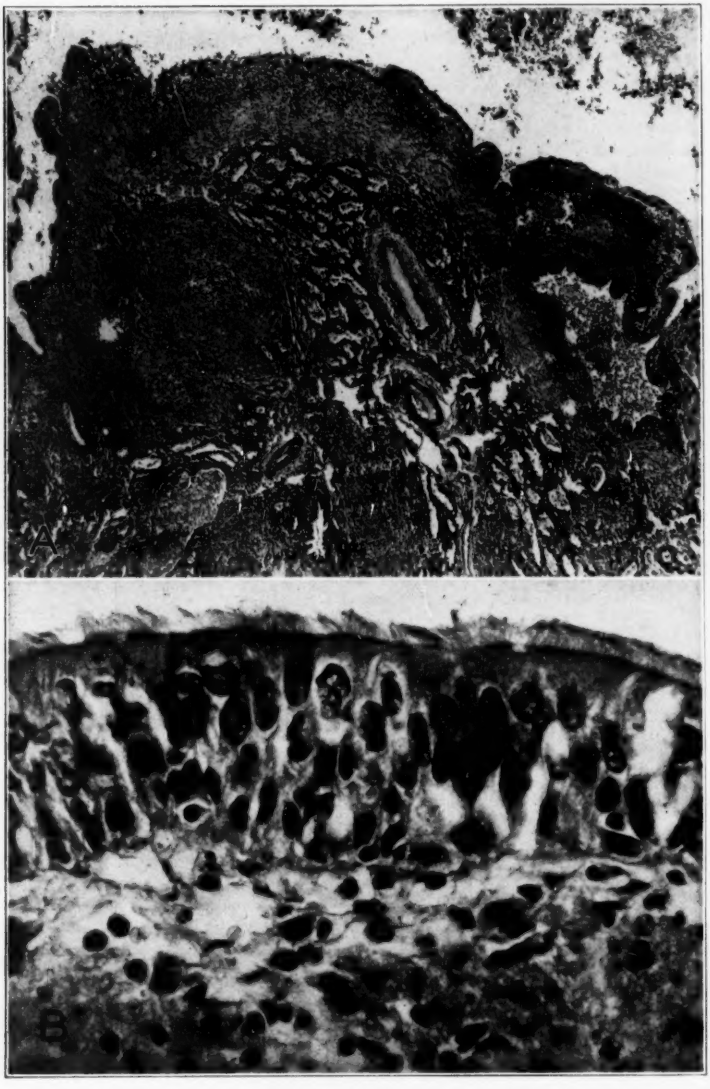

Fig. 4 (case 1).—*A*, photomicrograph of cyst wall; × 30. Most of the cyst wall is well preserved, and the basement membrane and lamellated fibrous tissue walls are plain. The smooth muscle is not visible with this power. Although the child was only 13 weeks old and had no clinical signs of infection, one area of the cyst wall is extensively ulcerated. The subjacent lung is greatly scarred. *B*, photomicrograph of cyst lining; × 600. The cilia of the pseudostratified columnar epithelium show plainly.

He was a thin, underdeveloped infant with pale skin and mucous membranes. There was no clubbing of the fingers. Over the left side of the chest was a wide area of increased percussion resonance and decreased breath sounds.

A roentgenogram (fig. 5) showed marked displacement of the heart and mediastinum to the right, with air in a large cyst occupying almost the entire left side of the chest. The left region of the diaphragm was displaced downward. In the bronchogram the left main bronchus was seen to end abruptly. There appeared to be no fluid in the cyst.

The preoperative impression was of a cyst in the upper lobe of the left lung.

Operation (July 16, 1946; excision of the lower lobe of the left lung, Dr. Ravitch).—The left hemithorax was found to be entirely filled by a large, round, smooth, bluish, thick-walled cyst containing air. The cyst was aspirated of 230 cc. of air. Even immediately after this aspiration it was not empty but was small enough to be delivered into the wound. It refilled rapidly with air, and it finally proved necessary to leave a large needle in situ. The cyst proved to involve the entire lower lobe of the left lung, while the upper lobe was completely atelectatic and displaced into the mediastinum. After removal of the lower lobe, the upper lobe expanded readily and filled the hemithorax.

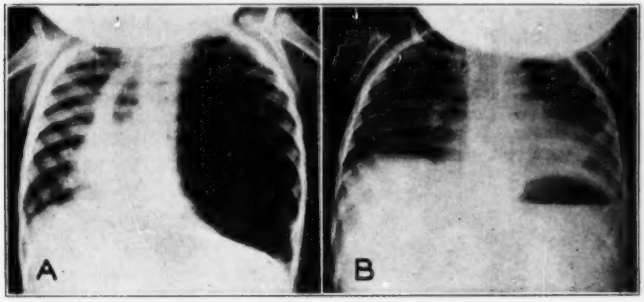

Fig. 5 (case 2).—The preoperative roentgenogram (*A*) shows the left hemithorax filled by an air-containing cyst which crosses the mediastinum and displaces the heart. *B*, three weeks after lobectomy. There is a little residual pleural thickening at the base of the left lung, the heart is back in position and the upper lobe of the left lung has expanded.

For several days after operation air accumulated in the left side of the chest. Otherwise the convalescence was smooth, and the lobe expanded well.

Pathologic Report.—The removed lobe is almost entirely occupied by a large, thin-walled, delicate cyst (fig. 6). Such epithelial lining as is left is low cuboidal. There is a thin smooth muscle layer and no visible mucous glands. The surrounding lung is scarred and compressed, forming a thin layer around the cyst. Here and there are fibrous septums projecting into the lumen like polypi (fig. 7). In a few places the cyst wall shows acute inflammation.

Course.—When last heard from, in November 1946, the patient was well.

Summary.—A year old infant had a huge air cyst of the lower lobe of the left lung filling the left side of the chest and displacing the mediastinum. Lobectomy was performed. A one way valve action was demonstrated at operation. Complete recovery resulted.

Fig. 6 (case 2).—Gross specimen. The cyst occupies all but a small segment of the basal portion of the lower lobe of the left lung.

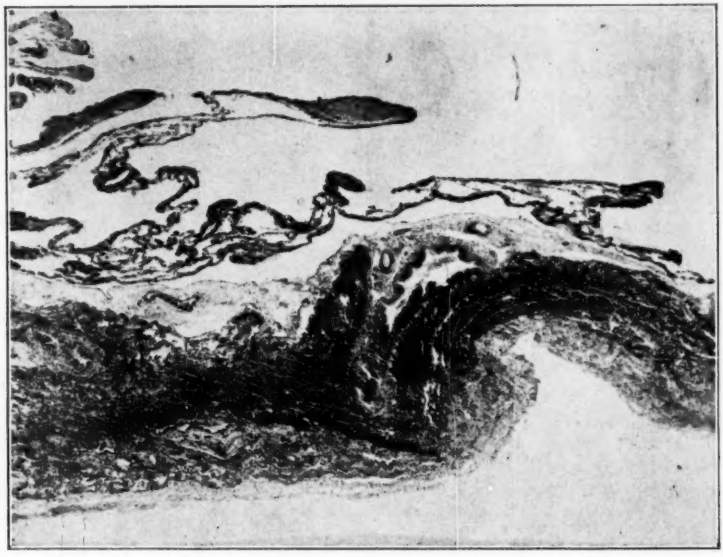

Fig. 7. (case 2).—Photomicrograph of cyst wall and lung; × 30. Full thickness of lung and cyst wall. The pleura is thickened and the lung collapsed and scarred. The cyst wall is thin. The epithelium lining the cyst is rather flat and covers the numerous septums which appear in the section almost like polypoid projections.

CASE 3.—D. C., a white female infant, was 8 months old on admission to the hospital. The baby weighed 6 pounds (2.7 Kg.) at birth but for the first week was too feeble to suck and had to be spoon fed. At 4 months she weighed 11 pounds (5 Kg.). There had been occasional attacks of spontaneous cyanosis, a few minutes at a time, up to the age of 4 months, when she had cough, fever and dyspnea, diagnosed as pneumonia. The roentgenogram showed multiple air cysts in the right upper area of the chest. Her temperature rose irregularly after subsidence of the first episode. Two months before admission to the hospital her temperature rose to 102 F. and remained there. A roentgenogram showed fluid-containing cavities in the lung, and multiple aspirations yielded foul pus, from which Staphylococcus aureus and nonhemolytic streptococci were cultured. The fluid levels finally disappeared.

On admission she was found to be a thin, weak, severely malnourished infant in no acute distress. The percussion note was dull, and breath sounds were diminished over the upper lobe of the right lung. There was no clubbing of the

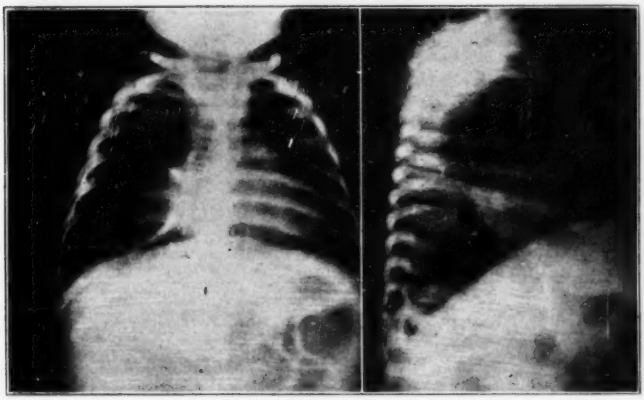

Fig. 8 (case 3).—Roentgenograms, anteroposterior and lateral views. At least two large cysts are seen filling the right hemithorax.

fingers. A roentgenogram (fig. 8) showed the entire right side of the chest filled by large air-containing cysts, with no fluid levels. The heart was displaced to the left.

The child was sent home (September 1939) to be "built up" and to return for operation in two years. However, in one month she died of lobular pneumonia.

Pathologic Report.—(The organs were forwarded for study.) The heart and left lung are normal. The lobes of the right lung are fused. At the apex is a large cystic cavity lined by delicate shining membrane. The largest cyst is 5.5 cm. The other cyst, a little smaller, does not communicate with it. The cyst wall is lined by granulation tissue, showing acute and chronic inflammation with occasional epithelial remnants. These are probably remnants of alveoli from the subjacent lung. These epithelial cells are low cuboidal. The substrate is dense scar tissue overlying the lung, which shows chronic inflammation.

Summary.—This was an 8 month old infant with severe constitutional symptoms from infected cysts, correctly diagnosed. Operation was deferred, and the patient died of a recrudescence of the pulmonary infection.

CASE 4.—D. N. was a white boy aged 2 years, 11 months. The child was apparently well until 14 months of age, when he had a respiratory infection for two weeks, diagnosed as bronchopneumonia. Two months later he had another bout of fever, dyspnea and malaise, lasting three weeks. For the subsequent six months he had repeated similar attacks, each lasting one or two weeks. He was thought to have unresolved pneumonia or possibly empyema or a pulmonary abscess. The condition was always localized in the right lung. When he was 2 years old a thoracentesis yielded 12 cc. of thick pus, and rib resection and drainage were performed. The cavity healed after a month, but the child soon after abruptly became febrile and the wound broke open and drained pus. There was no sputum.

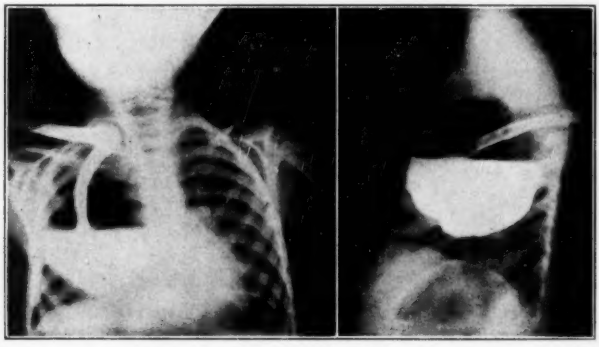

Fig. 9 (case 4).—Most of the right hemithorax is occupied by the large cyst, which is seen here partially filled with sodium iodide. The intercostal catheter had been inserted elsewhere to drain the "empyema."

Physical examination showed an undernourished child. There was a scar medial to the right scapula and a draining sinus at the level of the scapular spine. Iodized poppyseed oil 40 per cent instilled in the sinus outlined a large cavity occupying the position of the upper lobe (fig. 9). No bronchial communication could be demonstrated. Another rib resection was performed and another catheter inserted. The child coughed up methylene blue which was injected into the cavity.

He returned on October 1933, nineteen months after the onset, with the cavity unchanged and still draining.

Operation (Dec. 6, 1933, Dr. Rienhoff).—The smooth-walled cyst in the right lung was excised from the upper lobe by sharp dissection. Convalescence was fairly smooth, although the cavity was still draining at the time of the patient's discharge on Jan. 8, 1934. At present he is reported alive and well.

Pathologic Report.—The cyst is a saclike structure, 7 by 5 cm., with a smooth, glistening lining.

Microscopic examination (fig. 10) shows a well preserved epithelial lining varying from tall, ciliated, evenly columnar cells to pseudostratified columnar cells. A well defined basement membrane overlies the dense, scarred, fibrous wall in which are many lymphoid follicles and one lymph node. The adjacent

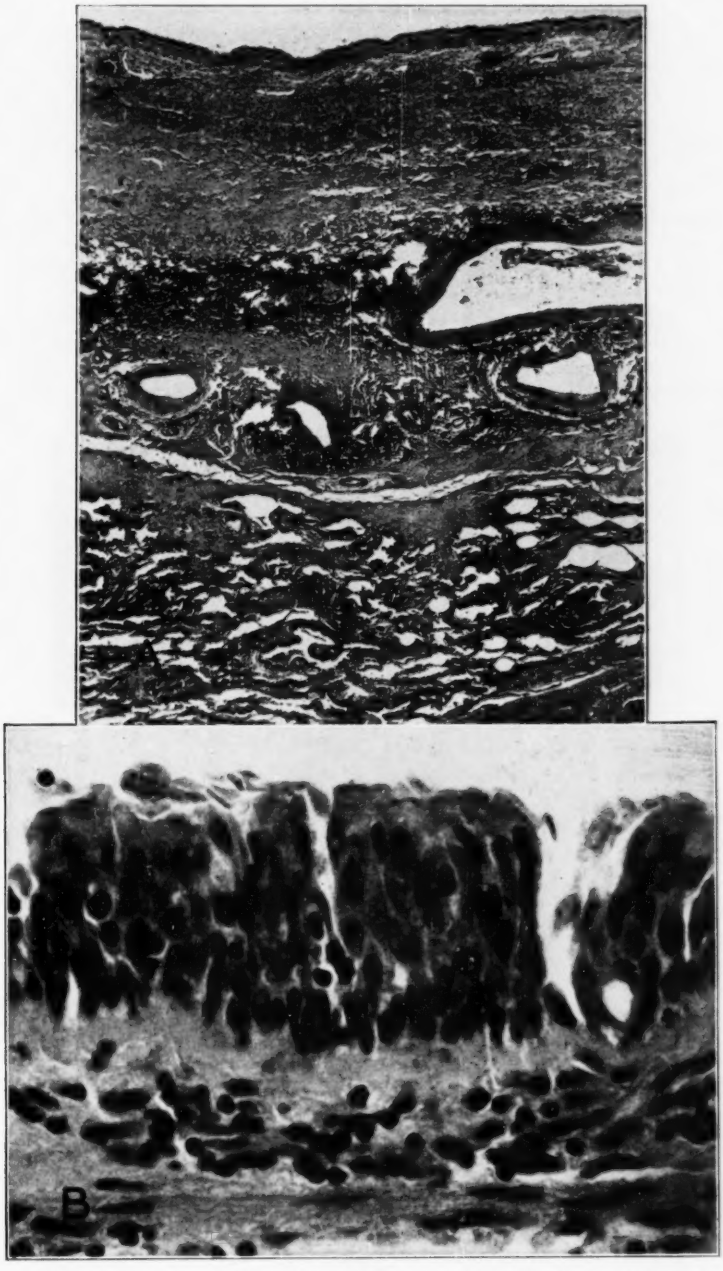

Fig. 10 (case 4).—*A*, photomicrograph of cyst wall; × 30. The epithelium is well preserved, and beneath it is a thick fibrous wall. It is difficult to tell whether the epithelium-lined spaces in the scarred subjacent lung are small cysts or merely isolated bronchi. *B*, photomicrograph of the cyst lining; × 600. The tall pseudostratified columnar epithelium is intact despite two years of catheter drainage.

lung is scarred and collapsed, and the numerous bronchi stand out in relief, as well as many irregular spaces, which might be construed as anomalous structures lined by bronchial epithelium.

Summary.—The child had been treated for almost two years for supposed chronic empyema, with repeated drainage. Excision of a unilocular cyst and partial resection of the upper lobe of the right lung were performed when the child was 3 years old. Despite the drainage and infection, the lining of the cyst is well preserved.

Case 5.—F. O. was a white boy aged 12 years. Five years before his admission he had a severe respiratory infection, diagnosed as pneumonia and followed by what was thought to be empyema. Six months later a rib resection and open drainage of the putative empyema were performed. A year and a half after

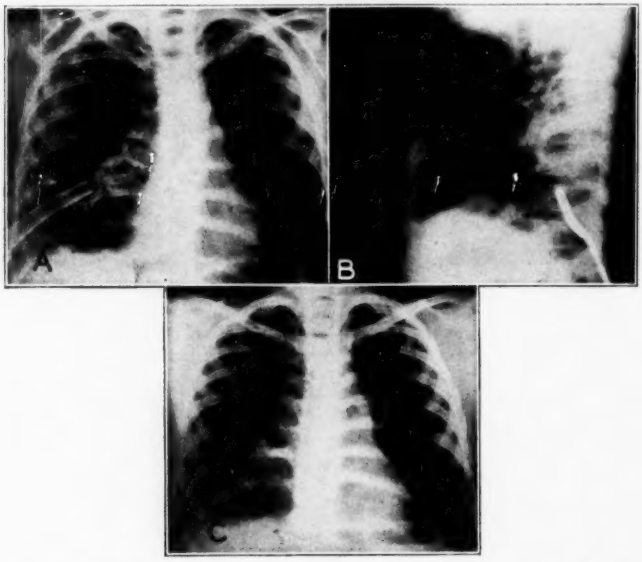

Fig. 11 (case 5).—*A* and *B*, preoperative roentgenograms show the catheter draining multiple radiolucent cystic areas in the lower lobe of the right lung. *C*, postoperative roentgenogram shows only residual pleural thickening.

this the chest was still draining, and a secondary closure of the cavity was attempted. The closure held for two months, when he became febrile, the cavity had to be reopened and for the first time a bronchopleural fistula was recognized. It was closed by cauterization, but the cavity persisted. The roentgenograms (fig. 11) were finally diagnosed as showing congenital cysts of the lung, and the child was sent to the hospital for operation. Iodized poppyseed oil 40 per cent injected into the trachea ran into numerous cysts.

Physical examination showed a vigorous boy of 12 years. There was no clubbing of the fingers. A depressed scar in the right posterior axillary line

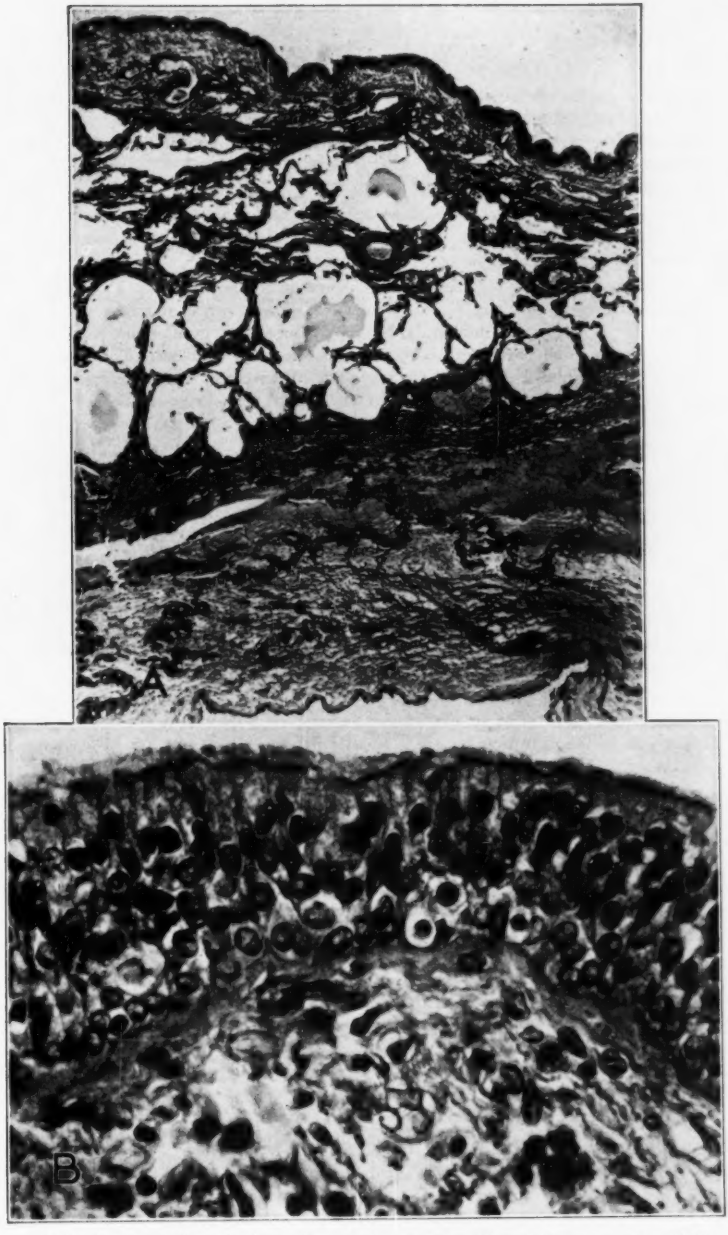

Fig. 12 (case 5).—*A*, photomicrograph of cyst wall and lung; × 30. Well preserved epithelium lines a relatively thin-walled cyst. The pleura is greatly scarred and thickened. *B*, photomicrograph of cyst lining; × 30. Pseudostratified columnar ciliated epithelium persists despite four and a half years of open drainage.

along the eighth rib surrounded an almost dry sinus 2 cm. in diameter leading into the chest. Slight dulness and suppression in the region of the scar and poor descent of the right side of the diaphragm were the only physical signs of thoracic disease.

Operation (May 13, 1944, Dr. Blalock; removal of the right lower and middle lobes).—The lower lobe alone appeared to be involved, but the middle lobe was removed because it was collapsed and atelectatic. Convalescence was smooth but for delayed expansion of the upper lobe.

Pathologic Report.—Just beneath the pleura on the anterolateral and posterolateral surfaces of the lung is a large cavity. When opened, it measures 12 by 15 cm. It is really multilocular, although the secondary cavities are small and mostly shallow and have large openings from the main chamber. The lining is thin, smooth, white and soft. Running along the surface in varying directions and curving and anastomosing in irregular fashion are numerous elevated, thin, cordlike thickenings of the lining. Some of these cords extend across the whole cyst from anterior to posterior and from lateral to posterior surfaces. The general consistency and appearance of these cords and cordlike elevations on the surface of the lining are much like those of the chordae tendineae of the heart valves. In the lumen there is a small amount of slightly opaque, pinkish fluid.

The cyst is lined by pseudostratified ciliated columnar epithelium, beautifully preserved in spite of the years of infection (fig. 12). Under the basement membrane is a layer of fibrous tissue beneath which the lung is only slightly scarred. There is no cartilage in the wall of the cyst, but there are remnants of smooth muscle. In a good many places there are small branches that grow off the main lumen of the cyst like little bronchioles, and these are clearly related to the underlying pulmonary structure.

Summary.—A 12 year old boy had a four and a half year history of repeated operations for drainage of an empyema and attempted closure of the cavity. In the lower lobe of the right lung he had a multilocular cyst which was lined by ciliated epithelium. He is well after resection of the lower and middle lobes on the right.

Case 6.—J. F. was a white boy aged 11 years, 3 months. A cyst of the lung was seen in a roentgenogram taken routinely when the child was in the hospital at 1 year of age for diarrhea. At 5 years of age, during an attack of pneumonia when he was extremely ill with high fever, a tube was inserted in the left side of the chest to drain the cyst. For the succeeding six years the tube was worn continuously. There was a constant slight discharge of glairy fluid, and there were the usual phenomena attendant on a bronchial fistula. He had no other pulmonary symptoms after insertion of the tube.

Physical examination on the patient's admission to the hospital showed a vigorous, well developed and well nourished boy of 11 years. There was a small rubber tube in a sinus in the left fifth interspace in the posterior axillary line. Through this tube a little glairy mucus was discharged, and on forced expiration air could be heard whistling through the tube. Respiratory excursions were diminished on the left, and there was dulness at this base.

Roentgenograms showed (fig. 13) a large, apparently unilocular, air-containing cyst occupying most of the lower lobe of the left lung and drained by a tube. Injection of iodized poppyseed oil 40 per cent into the cyst through the tube demonstrated connection with the bronchi, and a bronchogram demonstrated the cyst.

Operation (Oct. 17, 1946, Dr. H. W. Scott).—The cyst was densely adherent to the wall of the chest. When the sinus was clamped off within the

chest, the cyst filled rapidly under tension. Lobectomy was performed. Convalescence was smooth, and the boy was well at the time of discharge.

Pathologic Report.—Most of the lower lobe is occupied by a large, unilocular, rather fibrous-walled cyst with a smooth lining. At one point on the anterior surface is a short fistulous tract.

The cyst is lined by bronchial epithelium, tall, ciliated, columnar, with mucous glands beneath the lining (fig. 14 *A*). In several areas in the surrounding lung are large groups of bronchial glands proliferating in what appears to be adenomatous fashion (fig. 14 *B*). In one area these proliferating glands are seen to derive from the lining of the cyst (fig. 14 *B*).

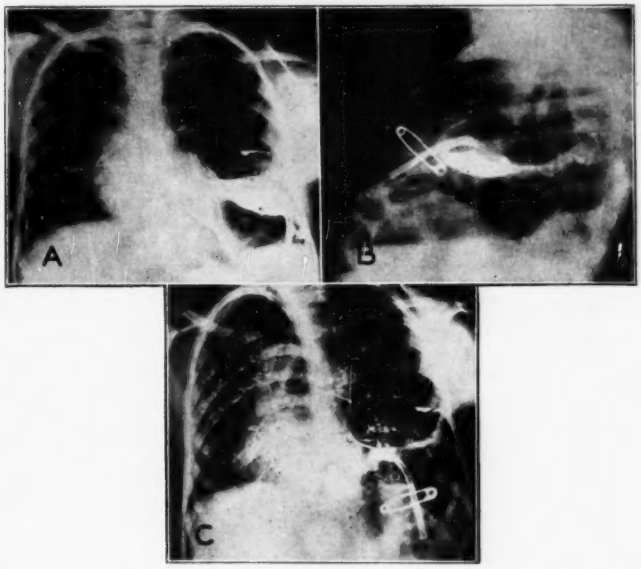

Fig. 13 (case 6).—Iodized poppyseed oil 40 per cent injected through the intercostal tube (*A* and *B*) and injected through the trachea (*C*) showing free communication between cyst and bronchial tree.

Summary.—An 11 year old boy was found at the age of 1 year to have a cyst of the lower lobe of the left lung. Frequent attacks of pulmonary infection culminated at the age of 5 in a severe episode, during which the cyst was drained. The drainage tube was maintained for the succeeding six years, with no symptoms but drainage and escape of air. At operation a valvular mechanism was proved. Resection of the lower lobe of the left lung effected a cure. The epithelial lining of the cyst was well preserved despite six years of drainage. Adenomas of mucous glands were found.

Case 7.—S. W. was a Negro girl aged 9 years. The child's birth and development were normal, and she was thought to be well until two months before her admission to the hospital, when she had what was apparently pneumonia, with a

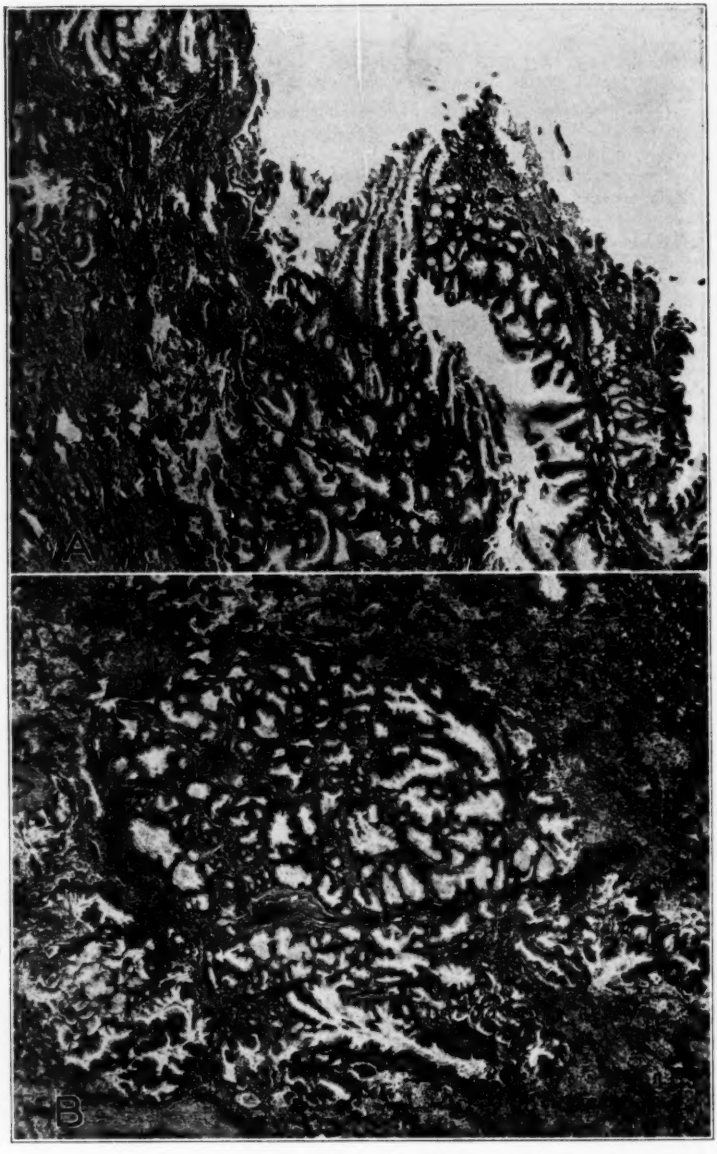

Fig. 14 (case 6).—*A*, photomicrograph of cyst lining; × 30. An adenomatous proliferation of bronchial glands can be seen deriving directly from the lining epithelium. *B*, photomicrograph of lung; × 30. Section taken at a distance from the cyst wall shows an area of adenomatous proliferation of mucous glands in the parenchyma of the lung.

temperature of 106 F., pleuritic pains and other symptoms. She recovered on sulfonamide therapy. Five days before admission she again had fever, cough and pain. Physical examination on admission showed a moderately sick girl with a temperature of 100 F. There were dulness and suppression over the lower lobe on the left and under the fluoroscope what was interpreted as dense opacity. Roentgenograms showed multiple radiolucent areas in the region of the lower lobe of the left lung (fig. 15). Her reaction to a tuberculin test was negative, and on penicillin therapy the fever and cough receded. Bronchograms (figs. 15 *B* and *C*)

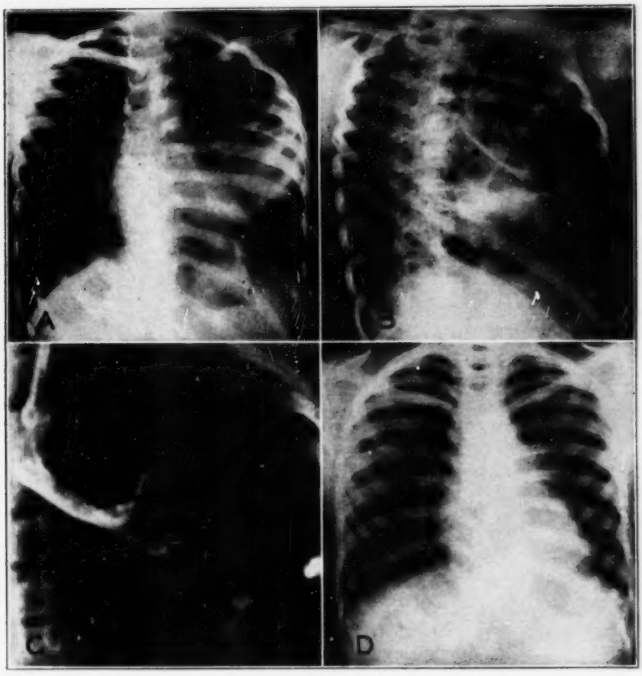

Fig. 15 (case 7).—Preoperative film (*A*) shows multiple cystic areas in the left mid-lung field. Bronchograms (*B* and *C*) show an anomalous bronchus arising from the left main bronchus and coursing upward before the division into upper and lower lobes. In (*B*) some lipiodol® has entered the cysts. The postoperative film (*D*) shows the normal appearance produced by expansion of the small anomalous segment of the upper lobe of the left lung.

showed the cystic areas in what was thought to be the lower lobe and the lingula of the upper lobe filled with iodized poppyseed oil 40 per cent.

Operation (Jan. 10, 1946, Dr. Ravitch).—There was found a trilobed left lung with a small upper lobe and two large remaining lobes, both involved in the cystic process. The rudimentary upper lobe was a slender pink structure about 5.0 by 2.0 cm. lying along the mediastinum and coming off the main bronchus

independently, its bronchus ascending sharply. This lobe was spared, the two lower lobes which were about equal in size being removed. The child convalesced satisfactorily, and almost at once the small lobe left behind filled the hemithorax. Fifteen months later the only evidence of her previous difficulty was the intercostal scar. Her chest was clear on physical and roentgenographic examination (fig. 15 *D*).

Pathologic Report.—All the upper lobe is occupied by a large multilocular cyst containing gray mucoid material. There are numerous small cystic areas in the remainder of the lung. Purulent material is present in the bronchi of the lower lobe, much of which has relatively normal parenchyma.

The cyst is lined by bronchial epithelium, some almost squamous and some ciliated. The walls were scarred with multiple septums which look, in section,

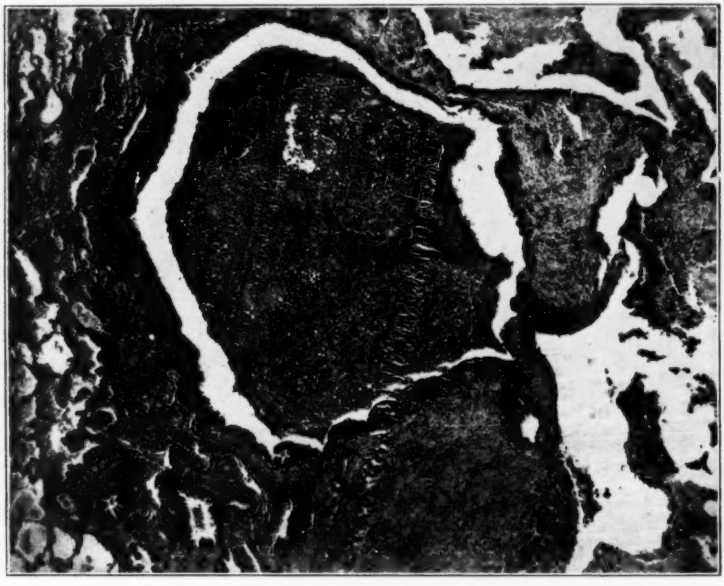

Fig 16 (case 7).—Photomicrograph of the cyst wall; × 30. The lining epithelium is intact, and one sees several cysts with connecting trabeculations. The underlying lung is scarred. Where the cyst wall is seen at a distance from a septum or trabeculation it is delicate.

like polypoid projections (fig. 16). Some of the scarring and organization in the lung is within the lumen of the bronchioles. Eosinophils are fairly numerous. Here and there a few smooth muscle fibers remain in the scarred cyst wall.

Summary.—A 9 year old girl suffered repeated attacks of pulmonary infection for two months. A bronchogram showed, in the lower lobe of the left lung, air-containing cysts which were injected with iodized poppyseed oil 40 per cent. At operation a trilobed left lung was found, with a small, uninvolved "upper lobe" coming independently off the main bronchus and corresponding to Broek's apical

and subapical segments. The two lower lobes were removed. Review of the bronchograms (fig. 15 *C*) shows distinctly an independent upper lobe bronchus coming off the main bronchus before its bifurcation. The pectoral and lingular segments formed the larger part of the remainder of the upper lobe and were the segments chiefly involved in the formation of the large cysts. The small apical segment filled the left side of the chest.

CASE 8.—W. B., a Negro boy aged 12½ years, was first seen on July 10, 1946. He had a twenty-four hour history of anorexia and a twelve hour history of pain in the epigastrium and the lower part of the chest. Fever was noticed just before he was brought to the hospital. He had a slight cough for twelve hours. His past history was entirely normal.

Physical Examination.—The temperature was 103 F. and the white blood cell count 10,000. The patient was a moderately ill Negro boy with signs of infection of the lower lobe on the left, diminished breath sounds, fine rales and diminished resonance.

Fluoroscopy showed an opaque area in the lower lobe of the left lung, with a fluid level. A roentgenogram (fig. 17 *A*) showed a dense infiltration extend-

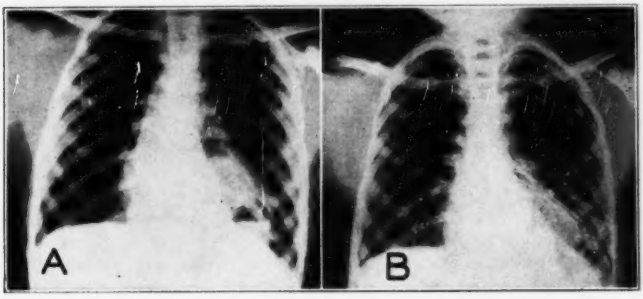

Fig. 17 (case 8).—*A*, roentgenogram showing fluid level in a radiolucent area in the lower lobe of the left lung. *B*, bronchogram; the lower lobe bronchi curve around the lesion. In a pulmonary abscess bronchi would tend to end abruptly at the lesion.

ing from the left hilus into the lower pulmonary fields. There was a radiolucent area within the area of consolidation representing a cavity with a fluid level. Bronchograms (fig. 17 *B*) showed the mass in the lower lobe displacing the bronchi. No iodized oil entered the cavity.

He was treated with postural drainage, penicillin aerosol and bronchoscopic aspiration on the supposition that he had an abscess of the lung. He was afebrile and asymptomatic by the sixth day, but treatment was continued for three more weeks, and on his discharge from the hospital he was asymptomatic although the roentgenograms were unchanged. He returned to school but was readmitted a month later with a slight nonproductive cough. Bronchoscopic findings and bronchograms were unchanged. It was thought that he might have an infected cyst of the lower lobe of the left lung.

Operation (Sept. 27, 1946, Dr. Scott and Dr. Ravitch).—The lower lobe of the left lung was found densely bound down to the diaphragm and the wall of the chest, from which it was cleared by sharp dissection. Three large separate arteries, varying in diameter from 4 to 6 mm., were found to enter the convexity

of the lower lobe posteriorly and were readily traced to their emergence from the aorta. These anomalous systemic vessels arising in a row from the aorta at intervals of a centimeter were each larger than the usual pulmonary artery to the lower lobe. The vessels were ligated and divided. There was no fissure between what were thought to be the lower and upper lobes, and after the bronchus and the vein had been secured (no ordinary pulmonary artery was seen with any certainty) the lobe was resected on clamps. It was now disclosed that although this left a portion of lung about as large as the usual upper lobe, there was an additional and separate lobe, completely distinct and not at all adherent. It was clear that we were dealing with a trilobed left lung. Reexamination of the preoperative bronchograms showed that there was an anomalous upper lobe bronchus coming off the left main bronchus before the dichotomous division into lower and upper. The anomalous lobe appeared to consist of Brock's apical and subapical divisions. The larger lobe adherent to the lower lobe was apparently composed of the pectoral and lingular divisions. The lower lobe was removed. Injection of the anomalous arteries produced a relatively normal pulmonary arteriogram, reversed in direction, all the fluid running readily out of the pulmonary vein at the hilus (fig. 18*A*).

The absence of any fissure between the lower lobe and the upper lobe produced a large raw surface. This was covered with interrupted sutures. It was then found that this so distorted the lobe that about a third of it could not be inflated. Therefore, the sutures were cut one by one until the lobe had expanded completely. This was a striking example of the occasional disadvantage derived from suture of the cut surface of the lung, a point emphasized by Churchill.

After operation the patient was initially febrile; thereafter, convalescence was uneventful.

Pathologic Report.—The specimen is a lower lobe of the left lung. The surface is rough and ragged, and on one side is a broad area of cut lung. On the convexity are three substantial arteries about 4 to 5 mm. in diameter, said to have arisen from the aorta. Within the lobe is a cavity filled with thick pus, the surrounding lung extensively indurated. The lining of this cavity proves to be ciliated epithelium, with many mucous glands in and under it in the surrounding layer of smooth muscle (fig. 18*B*). Although in some areas the lining is ulcerated and in one area there is a lining of granulation tissue, elsewhere the epithelium is perfectly preserved. Within the cyst and on its wall are seen particles of coal pigment. The subjacent lung is scarred and shows little but bronchial elements which frequently appear cystic and seem to be proliferating.

Summary.—A 12 year old boy with a brief history of pulmonary suppurative disease was found to have a cavity in the lower lobe of the left lung. At operation for cyst of the lung, suspected because of the persistence of the cavity after the infection had entirely subsided, he was found to have a trilobed left lung, the cavity being in the lowermost lobe and this lobe obtaining most or all of its arterial supply from three large anomalous vessels arising from the descending aorta and entering the convexity of the lower lobe. He has been asymptomatic since removal of the lobe.

CASE 9.—P. L. was a white boy aged 6 years, 5 months. At the age of 9 months he was seen at another hospital for pneumonia, which lasted three weeks. At 3 years he had fever and "bronchitis," and ever since he had cough at night and morning sputum, which he would swallow. Three months before his admission to the hospital he had two episodes of vomiting at night. "Often

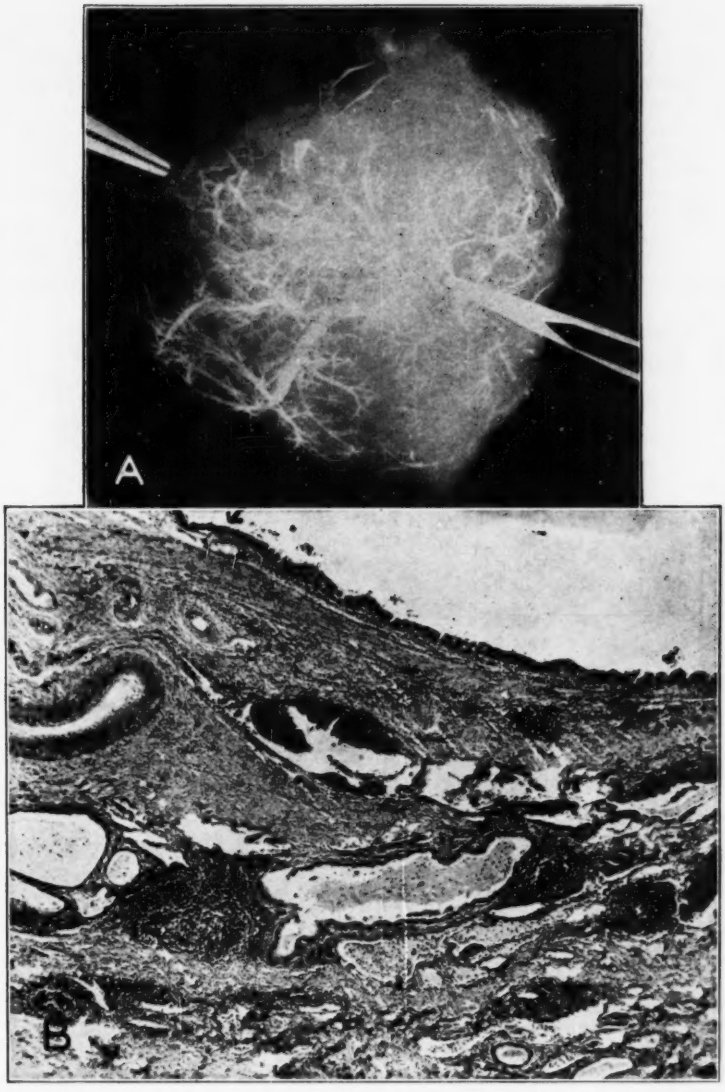

Fig. 18 (case 8).—*A*, roentgenogram of the specimen after injection of the largest anomalous artery with Hill's mass (by Dr. George Duncan). The hemostat is on the pulmonary vein at the hilus of the lobe. The orientation of the arteries is seen to be the reverse of the ordinary pattern. *B*, photomicrograph of cyst wall and subjacent lung; × 30. The characteristic epithelial lining is seen. Beneath the fibrous wall and apparently between it and the lung parenchyma are several cystic spaces lined with bronchial epithelium. The arrow points to a mucous gland beneath the cyst epithelium.

after doing somersaults he would cough up a greenish-whitish shimmering lump of material." The cough was worse at night, and often he had had bouts of dyspnea and noisy respirations.

Physical examination showed a fairly well nourished boy with a constant moist cough. There were diminished resonance and impaired breath sounds over the lower lobe on the right. A few fine post-tussic rales were audible. On fluoroscopy there was increased density at the right base, with two large round areas of radiolucency. The sputum contained type 14 pneumococcus.

Roentgenograms (fig. 19) showed at least three large cavities with fluid levels in the right lower lobe of the right lung. On bronchoscopy, greenish pus was seen to emerge from the bronchus of the lower lobe on the right. Alpha strep-

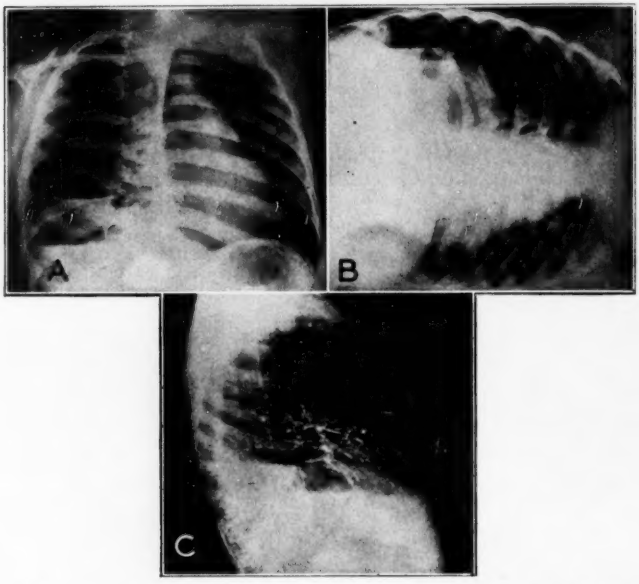

Fig. 19 (case 9).—Roentgenograms (*A* and *B*) of patient in upright and left lateral decubitus positions show fluid levels in cysts in the lower lobe of the right lung. Bronchogram (*C*) shows that lipiodol® does not enter the cysts.

tococci were cultered from the pus. Bronchograms (fig. 19 *C*) showed lateral displacement of the bronchi, with abrupt termination of the smaller bronchi. Iodized oil did not enter the cavities.

Operation (Sept. 27, 1946, Dr. Ravitch).—The lower lobe of the right lung was excised. A large systemic vessel, apparently arising from an intercostal artery, entered the convexity of the posterolateral surface of the lower lobe. However, there was found the usual pulmonary arterial branch to the lower lobe in its normal position. Recovery was uncomplicated.

Pathologic Report.—The specimen is a lower lobe of the right lung, firm and almost solid in many areas, with others rounded, cystic and bulging. A 5 mm.

artery enters the convexity of the posterolateral surface. On section the lobe is found to be almost entirely replaced by numerous large cysts, many of them intercommunicating (fig. 20) and all of them filled with thick glairy pus. In addition to the large cysts, 4 to 5 cm. in diameter, which were those seen in the roentgenograms, there are numerous smaller ones. The specimen was lost, and no microscopic sections were made.

Summary.—A 6 year old boy had a history of pulmonary infection from the age of 9 months. In the roentgenogram numerous cysts were seen in the lower lobe of the right lung, displacing and obstructing bronchi. At operation the lobe was removed and found to be replaced by cysts. An anomalous systemic vessel

Fig. 20 (case 9).—Gross specimen. The larger cysts intercommunicate, and bronchi can be traced into them. All the cysts contain thick glairy mucus.

arose from an intercostal artery and entered the convexity of the lobe. The boy has been well since operation.

CASE 10.—J. M. was a white girl aged 10 years. At the age of 5 years this child, who had had frequent sore throats and head colds, had a mild nonproductive cough and a low grade fever. In the next six to eight months the cough became productive of thick yellowish sputum. She had been in bed for months at a time ever since. Diagnosis of bronchiectasis of the upper lobe of the right lung was made elsewhere.

Physical examination showed a sallow, chronically ill, unhappy girl of 10 years. She was tachypneic and cyanotic at rest and had decided clubbing of the fingers and toes. Her respirations were labored, accessory muscles being used even at

rest. There were rhonchi in the right upper region of the chest and crepitant rales over both upper lobes, most notable on the right.

Roentgenograms showed clouding of the antrums and the ethmoid bones. Both pulmonary fields showed extensive infiltrative and fibrotic changes (fig. 21 *A*). Bronchograms (fig. 21 *B*) showed extensive saccular formations in the upper lobe of the right lung, with a pronounced tubular bronchiectasis of the lower lobe on the left and similar but less apparent changes in the lower lobe on the right.

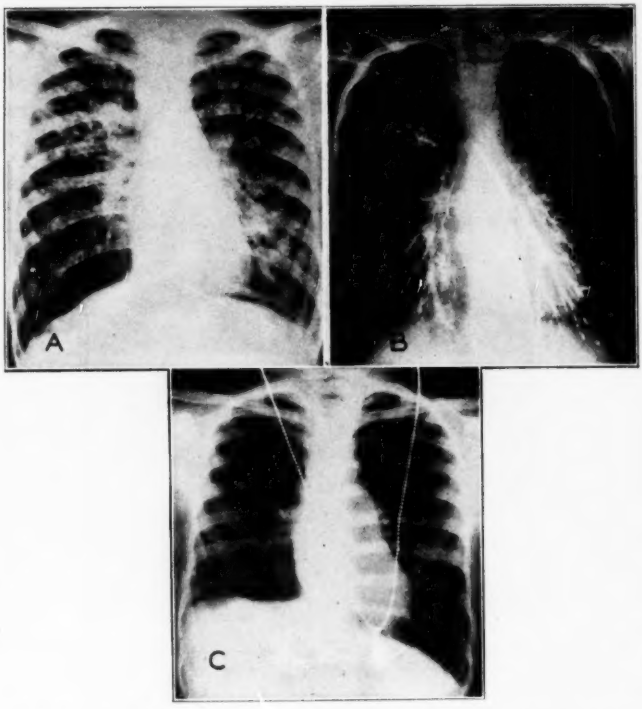

Fig. 21 (case 10).—Roentgenogram on admission (*A*) shows extensive infiltration in both lungs. Bronchogram (*B*) shows cystic bronchiectasis of the right upper lobe and bilateral tubular bronchiectasis of the lower lobes thought to be secondary to the process in the upper lobe. *C*, roentgenogram ten months after removal of the right upper and middle lobes. The chest is essentially clear.

It was impossible to be certain of the middle lobe. The patient was treated for six weeks with postural drainage, expectorants, steam inhalations, penicillin aerosol and penicillin intramuscularly and repeated bronchoscopic aspirations. Her sputum decreased, cyanosis and dyspnea lessened, fever disappeared and roentgenograms of the chest looked less frightening. Her vital capacity rose from 400

to 1,700 cc. It was thought that she had a congenital type of cystic bronchiectasis of the upper lobe of the right lung.

Operation (July 15, 1946, Dr. Ravitch).—Excision of the upper and middle lobes of the right lung was performed. The convalescence was smooth and the patient has made excellent recovery since, with practically normal exercise tolerance. She goes to school, rides a bicycle and has unrestricted activity. She has no sputum and almost no cough and shows no cyanosis or dyspnea. The clubbing of the fingers has receded considerably. Roentgenograms taken ten months after operation are essentially clear (fig. 21 *C*), and it begins to look as if the secondary bronchiectasis might regress without further operation.

Pathologic Report.—The lung is largely atelectatic, and numerous large bronchial spaces are seen. There are no features of the microscopic appearance affording certain differentiation from bronchiectasis. However, there are numerous large

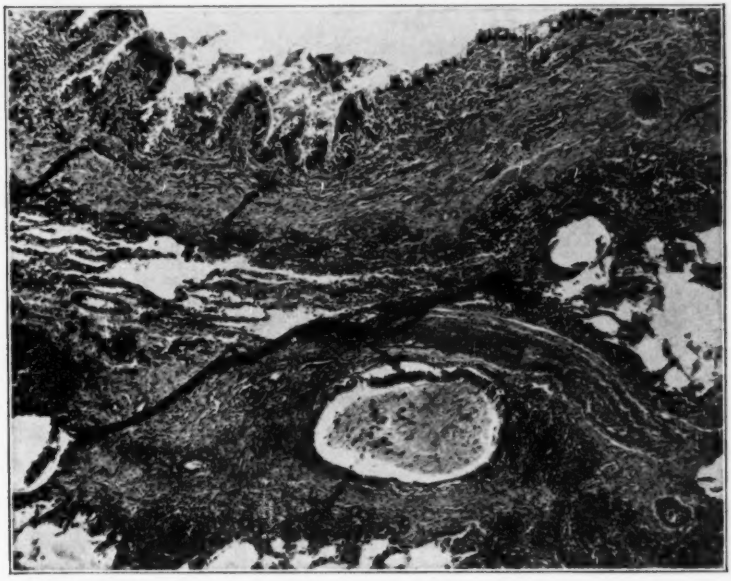

Fig. 22 (case 10).—Photomicrograph of a cyst wall; × 30. Typical bronchial mucosa. This is a large cavity, but no cartilage was seen in its wall. The occurrence of such smaller cystic spaces as seen in the photograph is at least suggestive.

bronchial spaces lined by infolded bronchial epithelium with remarkably little evidence of infection. Several large bronchus-like structures show no cartilage (fig. 22).

Summary.—A 10 year old girl had a five year history of cough and pulmonary disease. Roentgenograms showed a cystic type of bronchiectasis in an unusual location, the upper lobe of the right lung. Because of the location and the character of the cystic areas we thought we must be dealing with true congenital bronchiectasis or a type of cystic disease and not any ordinary secondary bronchi-

ectasis. The lower lobes on both sides showed a good deal of tubular bronchiectasis, which has subsided, in good part, since the removal of the principal offending lobe.

CASE 11.—H. H. was a white girl aged 6 years. She was first seen at the age of 20 months in September 1942 with a temperature of 103.8 F. and a twelve hour history of grunting respirations. She had had a "cold" for five days. There were physical and roentgenographic signs of pneumonia of the right lung, and she was admitted to another hospital. There a positive reaction to a tuberculin test was reported, and she was sent to a tuberculosis sanatorium, where she remained for six months. Her father was tuberculous.

She was seen again in October 1943 for a routine check-up. Physical examination revealed nothing abnormal, but roentgenograms showed fibrosis of the right apex, interpreted as being probably due to tuberculosis. Subsequent roentgenograms showed repeated infiltration of the upper lobe of the right lung, which, it was felt in the tuberculosis clinic, was not due to tuberculosis. The child was puny and poorly developed and had a constant cough. Over a space of three years the lesion persisted, as shown in numerous roentgenograms (fig. 23). The first bronchograms, taken in November 1946, showed extensive cystic or saccular dilatations branching out from the main bronchial tree of the upper lobe of the right lung (fig. 23 *B*). There was no demonstrable disease of other segments. Bronchoscopy showed reddening of the mucous membranes on the right.

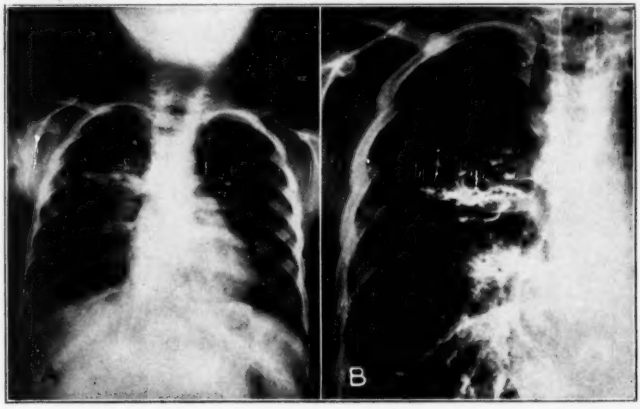

Fig. 23 (case 11).—*A*, roentgenogram; there is dense infiltration in the region of the upper lobe of the right lung. *B*, bronchogram; the cystic bronchiectasis is limited to the upper lobe of the right lung.

Operation (Jan. 20, 1947, Dr. H. W. Scott).—Resection of the upper lobe of the right lung was performed. Convalescence was uneventful, and the child has remained well since.

Pathologic Report.—The specimen is an upper lobe of the right lung which on section shows numerous dilated bronchi containing purulent material. The picture is indistinguishable from bronchiectasis on the basis of the microscopic examination. There are numerous large bronchus-like tubes in scarred lung.

The bronchial lining is well preserved, with little active inflammation and remarkably extensive epithelial infolding. In addition, in some areas there are numerous small round epithelium-lined spaces, probably regenerated alveoli (fig. 24). These are lined with low cuboidal epithelium and again show a surprising lack of inflammation.

Summary.—A 6 year old girl had symptoms of suppurative disease of the upper lobe of the right lung for more than four years. Bronchograms showed numerous saccules hanging from the bronchi of the main upper lobe like grapes from a stem. The picture was strikingly similar to that in case 10. We interpret the condition in both cases as congenital cystic bronchiectasis.

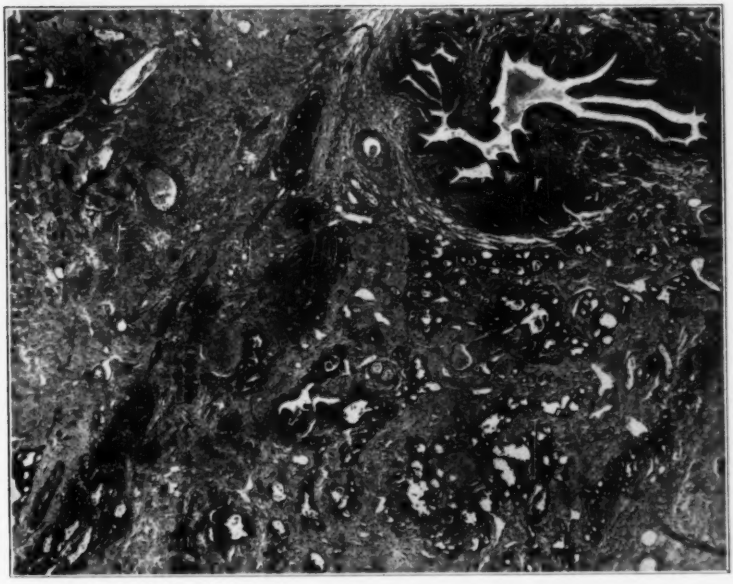

Fig. 24 (case 11).—Photomicrograph; × 30. Extensive infolding of the epithelium of the apparent bronchus. In the surrounding scarred lung are numerous cystic spaces which are probably regenerated alveoli. There is little evidence of active inflammation.

CASE 12.—R. H. was a white boy aged 13 years. At the age of 2 years he was alleged to have had pertussis and measles followed by bronchopneumonia. Ever since he had had a severe cough, productive of yellow sputum, particularly in the mornings. He had had a lifelong exertional dyspnea.

Five years before his admission to this hospital roentgenograms were said to show a pathologic process. He was never treated. He had had intermittent respiratory infections confining him to bed. His fingers had been clubbed as long as he could remember.

Physical examination showed a fairly vigorous boy of 13, slightly cyanotic, with rapid respirations (24 per minute) and pronounced clubbing of the fingers.

There was a slight respiratory lag on the left. The percussion note was impaired all over the left side, and the diaphragm in this area was elevated and fixed. Tactile fremitus was increased on the left, and there were whispered pectoriloquy and tubular breath sounds. A clicking noise was heard at the mouth. There were groaning, leathery rales all over the left region of the chest. The patient produced abundant sputum, from which were cultured Escherichia coli, Micrococcus catarrhalis and streptococci.

Roentgenograms (fig. 25) showed multiple, overlapping, round, radiolucent areas occupying the entire left lung and varying in size from 2 to 4 cm. A bronchogram (fig. 25 *B*) showed many of these cystic cavities filled with iodized oil.

Operation (March 30, 1946, Dr. Blalock).—Pneumonectomy was performed on the left side. The pleural cavity was found to be obliterated by dense adhesions. Recovery was rapid and uncomplicated.

The boy was last seen on Nov. 15, 1946. He had no cough, the clubbing had entirely disappeared and he played football with no undue dyspnea.

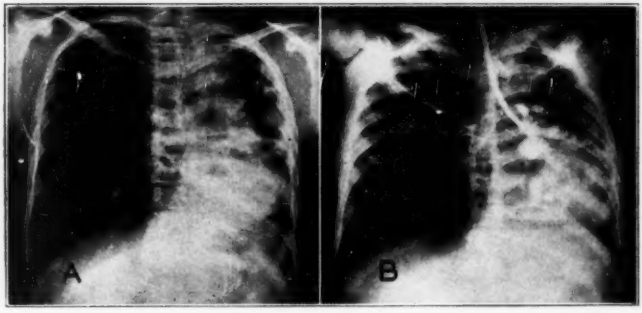

Fig. 25 (case 12).—Roentgenogram (*A*); the left lung is replaced by overlapping cysts. The lung is contracted and the heart drawn to the left. Bronchogram (*B*); several of the cysts closest to the hilus are filled with lipiodol.

Pathologic Report.—The specimen is a left lung, the pleural surfaces thickened and shaggy. The lung is firm and yellowish and shows numerous greatly dilated bronchi.

Microscopic examination shows numerous large spaces lined with well preserved bronchial epithelium, remarkably infolded. Definite bronchial glands are seen in some of these spaces. There are tremendous lymphoid infiltration and dense scarring around these structures. Despite the great size of these spaces none of them shows any cartilage in their walls (fig. 26).

Summary.—A 13 year old boy had pulmonary symptoms of considerable severity since the age of 2. Growth and development were not interfered with, as one would have expected them to be in bronchiectasis of this degree. The disease was entirely unilateral. The bronchogram of the right side was normal. The left lung was replaced entirely by innummerable cysts. Pneumonectomy was performed on the left side, with alleviation of all symptoms and disappearance of pulmonary osteoarthropathy.

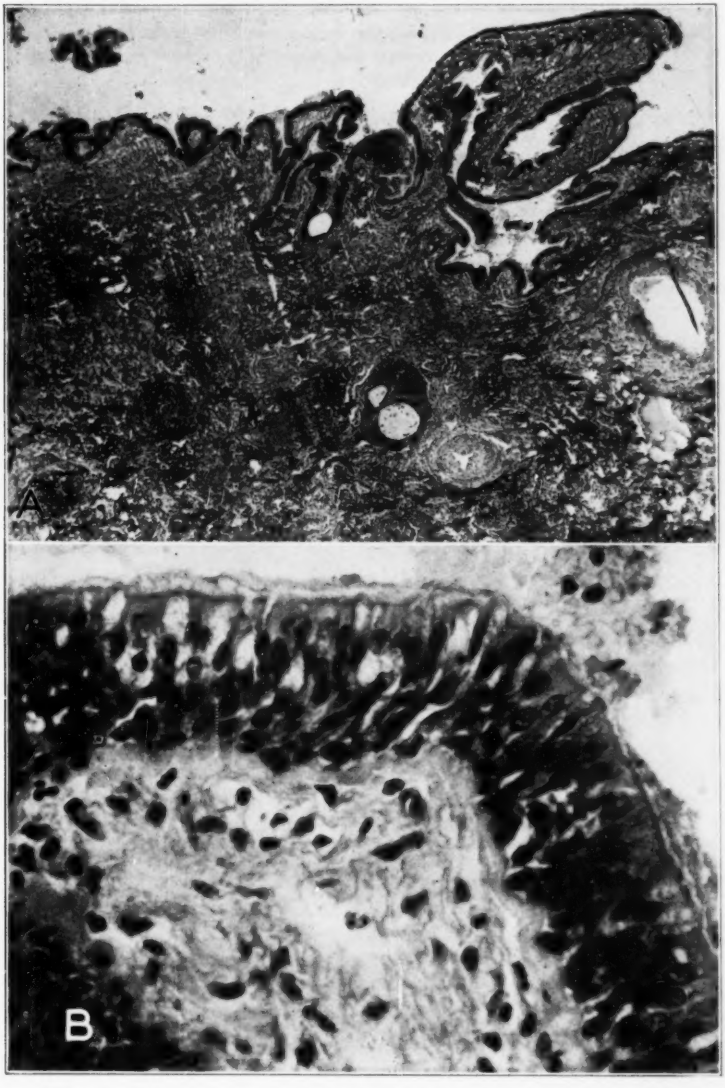

Fig. 26 (case 12).—*A*, photomicrograph of cyst wall; × 30. The almost polypoid character of the cyst walls is seen. The epithelium is well preserved and the lung beneath scarred. Although this is a large cyst there is no cartilage in its wall. *B*, photomicrograph of cyst lining; × 600. The epithelium is pseudostratified, tall and columnar and in this instance not definitely ciliated.

NOTE.—An additional patient has been operated on since this report was submitted. This was a 3 month old white male infant with cystic disease of the lower lobe of the right lung in whom it was necessary to perform pneumonectomy. The patient has done well since operation.

SUMMARY

Twelve patients suffering from cystic disease of the lungs are presented. They varied in age from 13 weeks to 13 years.

Some degree of infection was found in each case.

Eleven of the twelve patients were successfully treated by surgical removal of the involved area of lung (six single lobectomies, four lobectomies of two adjacent lobes and one pneumonectomy).

The single death, from pneumonia, occurred in an infant of 8 months for whom operation had been deferred and was not performed.

Among these 12 patients, 2 were found to have cysts associated with anomalous lobes of the lung, in each instance a trilobed left lung; 1 of these had an anomalous arterial blood supply derived from the aorta. A third patient had an anomalous systemic artery entering a cystic lower lobe of the right lung.

Resection of the cyst or of the cyst-bearing segment of lung is the recommended treatment.

BLEEDING PEPTIC ULCER

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BALTIMORE

AMONG the many wound stripes incident to modern civilization perhaps the one which looms most prominent yet remains most perplexing is the problem of peptic ulcer and its perilous complications. About 8,800 persons die annually in the United States alone from the sequelae of peptic ulcer, and massive hemorrhage due to ulcer is a grim contributor to this excessive toll.

Recent therapeutic procedures in the treatment of peptic ulcer have produced many changes of opinion. However, there still remains much controversy over the treatment of gastroduodenal bleeding. Is surgery indicated and, if so, for which patients? When is the optimal time to operate and what is the operation of choice? What is the present status of transfusions and parenterally administered fluids? Is morphine contraindicated? Is it best to feed patients promptly or to starve them? What is the current trend in antacid therapy? Are amino acids helpful? Is vagotomy the sovereign remedy in bleeding peptic ulcer?

In regard to none of these important issues is there general unanimity of opinion. Dogmas which were formerly held in high esteem have now been discarded, only to be supplanted by doctrines which long ago were regarded with doubt and distrust. Every case of hemorrhage caused by ulcer must be considered on its own merits. There are no hard and fast rules for prudent guidance, as clinical judgment is based on individual experience. However, data collected from mass statistics call attention to the best results of treatment and favor medical progress toward this general attainment.

Thus, the present misgivings concern many phases of the problem of bleeding ulcer—the origin and nature of the lesion itself, the status of medical and surgical treatment, the present prospect for a permanent cure and the successful management of the common complications of peptic ulcer, namely, massive hemorrhage, perforation, obstruction and alkalosis.

The present study of bleeding peptic ulcer is based on a statistical analysis of all patients with gross hemorrhage from an ulcer who have

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From the Department of Surgery, Johns Hopkins Hospital.

Read before the Forum on Fundamental Surgical Problems, Clinical Congress of the American College of Surgeons, Sept. 9, 1947.

been admitted to the Johns Hopkins Hospital since 1928, that is, all patients with the exception of infants and children who were seen in the pediatric wards with acute gastroduodenal ulcers and massive exsanguinating hemorrhages. These youngsters had acute ulcers of a distinctive type (perhaps analogous to Cushing's or Curling's ulcer in an adult), but the picture presented was otherwise unlike the characteristic clinical picture which we associate with chronic peptic ulcer. Instances of acute erosions of the gastroduodenal mucosa were eliminated from this study whenever this diagnosis was suspected.

From a review of the medical literature it is evident that there is a great divergence of concept regarding treatment and even a greater claim and counterclaim of mortality rates among the champions of a cherished type of therapy for hemorrhage due to ulcer. Certainly much of this difference of opinion must result from the comparison of collected cases which are not at all similar in the severity of the bleeding. In recognition of this fact alone, efforts are constantly being made to discover a more exact method of determining true loss of blood. Only then can a real assessment of the progress of bleeding ulcer be ascertained and reliable evaluation of contrasting measures of treatment be accurately judged. Also, the possible development of newer diagnostic aids which will foretell the location of an ulcer and estimate the caliber of the artery bleeding in its base would be of great value in determining the type of therapy best suited to this imminent source of danger.

INCIDENCE

By definition all patients in this series had gross hemorrhage from ulcer in contrast to occult bleeding. Spontaneous vomiting of "coffee ground" material, red blood or the passage of a black, tarry stool depended for quantity on the extent and severity of the hemorrhage. Although it has been shown by several investigators that as little as 60 cc. of ingested blood can be sufficient to cause a tarry stool, yet the average patient hospitalized because of a bleeding peptic ulcer usually showed a much more pronounced degree of loss of blood.

In the period between 1928 and the first part of 1946 (table 1) there were 2,400 patients admitted to the Johns Hopkins Hospital with a diagnosis of duodenal, gastric or marginal ulcer. Many of these patients were admitted to the hospital many times; however, the number of patients, and not the number of admissions, was tabulated. During this same period there were 218 patients with active hemorrhage from ulcer admitted to the hospital. Thus, about 9 per cent of patients with ulcer who required admission to the hospital did so because of gross hemorrhage. This corresponds reasonably well with the reports from other large medical centers. Kirsner and Palmer at the University of Chicago

reported an incidence of massive hemorrhage of 10.6 per cent, Eusterman reported gross hemorrhage in 17 per cent of the operative cases of ulcer at the Mayo Clinic and Heuer noted that 21 per cent of the patients with ulcers admitted to the New York Hospital entered chiefly because of hemorrhage. It is, of course, difficult to estimate the actual incidence of bleeding from ulcer as only about 10 or 20 per cent of all ulcer-bearing patients ever find it necessary to be hospitalized.

Annual Incidence.—In figure 1 the annual number of patients with bleeding ulcer are charted according to the yearly rate of admission to the hospital. During the period 1928 to 1935 the catalogue of diagnoses appears to be incomplete and the total number of cases of hemorrhage from ulcer is probably fragmentary. However, from the annual rate of admissions it could not be concluded that the mental and physical strain of World War II predisposed patients with ulcer to increased hemorrhage.

TABLE 1.—*Patients with Ulcer Admitted to the Johns Hopkins Hospital Between 1928 and 1946*

Ulcer		Bleeding Ulcer
1,510	Duodenal	156
833	Gastric	25
57	Marginal	5
.....	Combined	8
.....	Unknown	24
Total 2,400		218

Monthly Incidence.—It is, of course, widely known that the pangs of peptic ulcer are less prevalent during the summer months, and this is also reflected in the lowered incidence of hemorrhage from ulcer (fig. 2). Definite seasonal exacerbations are known to occur in duodenal ulcer during the early spring, late fall and early winter months. The reason for this seasonal periodicity has never been satisfactorily explained, although Crohn and Shwartzman expressed the belief that massive hemorrhage from ulcer may be due to a local Shwartzman phenomenon from infections of the upper respiratory tract, which are most common during the spring and late fall. Lisa and Likely reported 5 cases of chronic peptic ulcer and death from exsanguinating hemorrhage in which bacterial infection of the wall of an artery was demonstrated in each case. Harkins in 1938 studied the problem of acute ulcer of the duodenum as a complication of burns—the eponymic Curling's ulcer—and reported its relation to sepsis.

RACE AND SEX

The sex incidence (fig. 3) among the present series reveals the proportion of males to females in the whole group to be 5.2 to 1. However, it is of interest to note that of the 16 patients who died 15 were males and only 1 was a female.

The ratio of white to Negroes was 2.3 to 1, which may be explained by an equivalent difference in the bed capacity at the Johns Hopkins

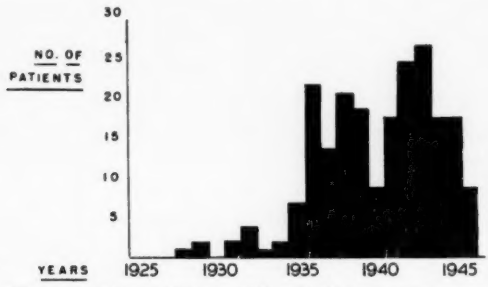

Fig. 1.—The period from 1935 to 1946 probably represents a more accurate record of the annual number of patients with bleeding peptic ulcer admitted to the hospital.

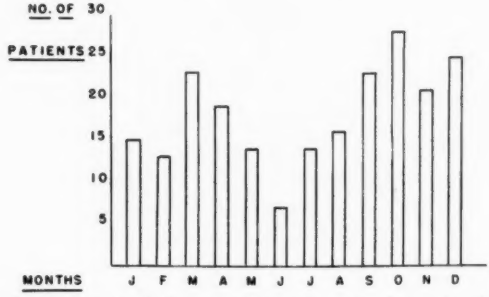

Fig. 2.—Seasonal exacerbations are known to occur in peptic ulcer, and this fluctuation is also reflected in the monthly admissions of patients with hemorrhage from ulcer.

Hospital for the respective races or perhaps accounted for by the racial distribution of Baltimore, which is approximately in the proportion of 4 whites to 1 Negro.

AGE

Among the varied factors which affect the seriousness of hemorrhage from ulcer age has been shown by many investigators to be highly impor-

tant. Experience at the Johns Hopkins Hospital (fig. 4) corroborates the fact that hemorrhage from ulcer is more likely to be serious or fatal among patients past 50; in 150 patients under the age of 50 the mortality rate was only 5.3 per cent, whereas in 68 patients above the age of 50 the mortality rate was more than doubled—11.8 per cent. However, it is important to note that there were 8 fatalities among patients under the

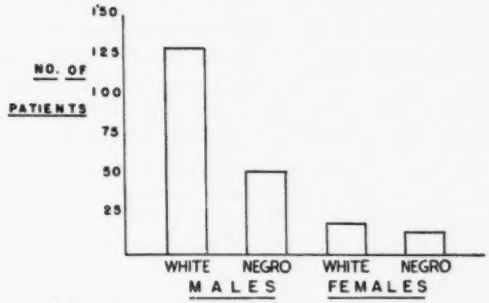

Fig. 3.—The proportion of males to females in the entire group is 5.2 to 1. However, it is of interest to note that of the 16 patients who died, 15 were males and only 1 was a female.

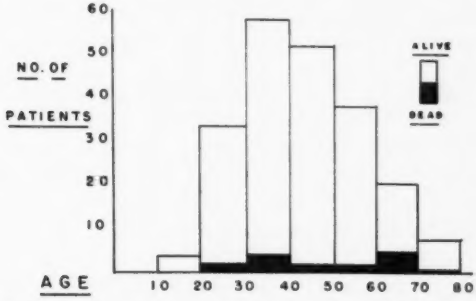

Fig. 4.—In 150 patients with bleeding peptic ulcer who were under the age of 50 the mortality rate was only 5.3 per cent, whereas in 68 patients above the age of 50 the mortality rate was 11.8 per cent. The highest mortality rate occurred in the sixth decade.

age of 50, and that 4 of these died while comparatively young, i. e., while in their thirties. Thus, even young patients with elastic arteries may die of hemorrhage from ulcer, for youth alone is no guarantee of hemostasis.

Most cases of hemorrhage from ulcer occurred in the third decade of life. However, more than half of the entire series (112 patients) ranged in age between 30 and 50 years.

BLEEDING

The exact assessment of the severity of hemorrhage from ulcer is by no means easy. The amount of blood vomited or passed through the bowel can rarely be accurately measured. Thus, since there are no precise criteria for the classification of early hemorrhage the present group of cases was divided grossly according to (1) available laboratory tests, (2) the clinical picture and (3) the house staff's recorded impression of the amount of blood lost.

It has been shown by Blalock and others working in the field of shock that loss of blood or plasma is a most significant initiating factor in the production of shock. A decreased blood volume and reduced circulation caused by massive or prolonged hemorrhage from ulcer bring about the various physiologic and clinical changes which are the sustaining factors in shock. Copious bleeding leads to tissue anoxia, increased capillary permeability and irreversible peripheral circulatory collapse. Fatal shock, with characteristic hemoconcentration and pathologic changes in the tissues, can be produced even by slow persistent bleeding.

TABLE 2.—*Extent of Bleeding Among Patients with Ulcer*

	Number	Deaths	Per Cent
Moderate	83	2	2.4
Massive	102	12	11.7
Minimal	32	2	6.2
Unknown	1	0	...

It does not seem to matter whether the hemorrhage is outside the body or into the gastrointestinal tract, as in cases of bleeding ulcer, as far as the production of shock is concerned.

In the absence of simple and reliable methods of determining the effective circulating blood volume, clinical judgment alone is difficult and estimation of true loss of blood (when determined early) may even be misleading. The initial blood counts and hemoglobin determinations are not accurate indexes of the severity of bleeding because it may be several days before blood volume can be again restored to normal and only then can the magnitude of actual loss of blood be measured. Clinical signs of reduced blood volume are mainly to be found in alterations of blood pressure and impaired physiologic functions incident to a decreased blood flow.

In the present series (table 2) gross hemorrhage from ulcer was divided into three groups: moderate, massive and minimal, depending primarily on the stated impression of the severity of the loss of blood as recorded in the history. This means of classification was further verified by the clinical condition of the patient and the routine laboratory studies

of the blood. In accordance with every reasonable expectation, the highest mortality rate occurred in the group of cases in which the hemorrhage was classified qualitatively as massive.

AZOTEMIA

Greater vigilance and clinical alertness in the medical observation of cases of bleeding ulcer may be augmented by estimation of the increase in blood urea. Often the simple cases of hemorrhage from ulcer may be sifted from the severe cases by means of this helpful expedient. Massive hemorrhage into the gastrointestinal tract causes an increase of blood urea occasionally to uremic levels. There is usually oliguria and sometimes anuria. The urine may show a good concentration of urea, but the specific gravity is not as high as might be expected.

Although the actual mechanism of this alteration of blood chemistry is obscure, it has been reported by some observers that the rise in blood urea closely parallels the degree of hemorrhage into the intestinal tract. Borst attributed the azotemia to the rapid absorption of urea formed from the blood in the intestinal tract. However, Johnson administered whole blood by stomach tube in amounts up to 1,500 cc. and noted a marked increase of blood urea in only 1 patient, who had impaired renal function.

Witts expressed the belief that the increase is due to the fall in blood volume which reduces the blood flow through the kidneys. This occurs at a time when the kidneys have the extra work of excreting a large amount of nitrogenous products derived from blood which is in the intestine. Yet, other investigators found the rise of blood urea nitrogen less closely related to the severity of the hematemesis, melena or anemia. Regardless of the uncertainty of its origin, the azotemia usually occurs promptly within the first day or two of hemorrhage from ulcer and may be used, within limits, as a guide in charting the course and management of a bleeding peptic ulcer. It appears probable that the azotemia is due to the combined effects of reduced blood volume, lowered blood pressure, the dehydration associated with hemorrhage from ulcer and the added waste products from the breakdown of blood.

PAIN

Several of the British surgeons, among them notably Gordon-Taylor, have stressed the importance of severe or intractable pain as a precursor of ill-boding in cases of hemorrhage from ulcer. The presence of excruciating pain preceding active bleeding and persisting afterward is considered a bad omen, and its prognostic significance favors urgent and early surgical intervention during the period of active hemorrhage. From the experience in this hospital (table 3) one cannot confirm this

belief or even conclude that severe pain is a Cassandra in cases of hemorrhage. Little significant difference in mortality statistics was noted regardless of whether severe pain was present or not.

HISTORY OF ULCER

In the present series of 218 patients with hemorrhage from peptic ulcer (table 4) more than 75 per cent gave a characteristic clinical syndrome of typical chronic ulcer. Less than 25 per cent failed to give an orthodox history of ulcer prior to the onset of bleeding but were found to have an ulcer on further careful study or at operation.

Although it is more or less commonly believed that the mortality rate increases with each recurring hemorrhage from ulcer, the present series

TABLE 3.—*Relation of Pain to Mortality*

	Number	Deaths	Per Cent Mortality
Severe pain with bleeding	66	6	9.0
Severe pain before or after bleeding	4	0	0.0
No severe pain	147	10	6.8
Unknown	1	0	0.0

TABLE 4.—*History of Ulcer* *

Previous ulcer history	165
No previous ulcer history	53
Previous history of bleeding ulcer	108
No previous history of bleeding ulcer	108
Unknown	2

* Patients whose history indicated recurrent hemorrhage had about the same fatality rate as those admitted during their first attack of bleeding.

fails to verify this belief. Patients whose history indicated recurrent hemorrhages had about the same fatality rate as those admitted during their first attack of bleeding. Kirsner and Palmer found that "the mortality rate was approximately as high in the first hemorrhage as in subsequent hemorrhages." Allen and Benedict reported that "60 per cent of our fatal cases died during their first episode of bleeding." Thus, although it has been rather a hackneyed dogma to say that no patient ever dies from his first hemorrhage from ulcer, the facts belie the truth of this specious reasoning.

DIAGNOSIS

The difficulties encountered in the differential diagnosis of gastroduodenal bleeding are apparently more perplexing to the medical writers of other countries than they are to American physicians. Holman, from a study of cases of bleeding ulcer at the New York Hospital,

stated that "the commonest cause of bleeding from the stomach or duodenum is peptic ulcer, and this diagnosis can usually be made after such other possible causes as esophageal varices, cancer and the hemorrhagic diatheses have been excluded." On the other hand, Witts, Physician in Charge of Medicine at St. Bartholomew's Hospital in London, found that gastroduodenal bleeding was due to peptic ulcer in only 37 per cent of the cases and in the remainder of the group it was due to acute erosion, gastritis and cirrhosis.

Perhaps the fact that it is difficult to distinguish accurately between gastritis, acute erosions and chronic ulcers has been responsible for certain discrepancies noted in the reports of so-called comparable series of cases of bleeding ulcer. There can be no doubt that in cases of hemorrhage resulting from acute erosion or gastritis the mortality is negligible, whereas in cases of hemorrhage from chronic ulcer the mortality is high. Gastritis appears to be far more common in England and the continental countries than in this country, and by its very nature and its great similarity to the clinical picture of chronic ulcer it may often be mistaken for it. Gastroscopy alone settles the diagnosis, but in the presence of gastroduodenal bleeding such a procedure is not without hazard.

TABLE 5.—*Complications Among Patients with Bleeding Ulcer*

	Number	Deaths	Per Cent Mortality
Obstruction	22	2	9.0
Severe anemia	108	13	12.0
Slight anemia	110	3	2.7
Arteriosclerosis	53	9	16.9
No arteriosclerosis	165	7	4.2

COMPLICATIONS

It is needless to say that in dealing with bleeding peptic ulcer it is of the utmost importance to determine, if possible, in which case hemorrhage from ulcer is likely to cause death if unchecked by surgical intervention and, conversely, which ulcer will cease to produce hemorrhage under proper conservative therapy. In pursuit of an answer to this problem, several common complications of bleeding ulcer were studied and their respective mortality rates determined (table 5).

Pyloric obstruction causing considerable retention of gastric contents and evidenced clinically by vomiting or by visible gastric peristalsis or objectively demonstrated by roentgen examination caused no significant increase in the death rate.

Serious hemorrhage causing severe anemia as contrasted with slight anemia (3,000,000 red blood cells, with hemoglobin 50 per cent, or 7.5 Gm. per hundred cubic centimeters, and the clinical evidences of

prostration and shock being the arbitrary dividing line between severe and slight anemia) caused rather a sharp difference in the mortality rates. Exsanguination causing severe anemia resulted in 13 fatalities in 108 patients, whereas passive bleeding or slight anemia resulted in only 3 deaths in almost the same number of patients, a rather striking difference. Cullinan and Price have suggested that the gradient of the drop in hemoglobin and red blood cell values, rather than the actual values, may indicate more clearly the severity of bleeding. This gradient was not studied in the present series.

Arteriosclerosis, noted in the record of 53 patients, appeared to have rather a profound effect on the mortality rate. However, the fact that brisk hemorrhage may be occurring through an eroded arteriosclerotic artery can be only part of a springtide story. The vicious cycle of impaired renal blood flow, cardiorenal complications and the azotemia of gastrointestinal hemorrhage acts to aggravate further a high mortality rate.

Thus, it seems that the common complications of hemorrhage from ulcer are merely straws in a shifting wind and can be only in a limited sense used as a trustworthy guide in determining the most desirable therapy for the patient with bleeding from a peptic ulcer. Indications for treatment depend on a clearcut classification of the type of bleeding which is encountered. It is unfortunate, however, that such a clearcut clinical criterion designating the specific patient with uncontrollable hemorrhage from ulcer remains yet to be found. Patients enter the hospital in every stage of physical reaction and debility due to hemorrhage. Their physiologic response to loss of blood is notoriously different, and the selection of patients whose hemorrhage is likely to prove fatal if not surgically checked as contrasted with those whose hemorrhage is likely to cease spontaneously is still a problem.

TREATMENT

Until recently the treatment of peptic ulcer and its complications was generally conceded to be medical. Differing opinions concerning the etiology and pathogenesis of peptic ulcer naturally resulted in a procession of differing therapeutic panaceas. Many of these enjoyed momentous popularity until a recurrent hemorrhage or ulcer niche was found at the end of the rainbow. The evaluation of any ulcer regimen is difficult because many ulcers heal with little or no treatment. Moreover the clinical course of the disease is characterized by variable periods of remission and exacerbation.

Also, the psychosomatic effect of any new drug may lead to a temporary relief of symptoms and an ensuing period of good health. As pointed out by both Eusterman and Heuer, the general principles of treatment of hemorrhage from ulcer are based on the physiologic treat-

ment of hemorrhage anywhere. Medical management consists of complete physical and mental rest, the frequent feeding of a soft, nutritious diet, administration of antacids, the intravenous use of dextrose, isotonic sodium chloride solution and amino acids, plasma and blood transfusions, sedatives, antispasmodics and narcotics and all other ancillary measures indicated. Whether the current trend toward section of the vagus nerve will alter these basic principles of treatment remains to be seen, for at the moment we are in that interminable "interval between the seed and the timber."

Medical Treatment.—Narcotics: Among the more common derivatives of opium, morphine was used most frequently at the Johns Hopkins Hospital to induce quiet and relieve anxiety in patients with hemorrhage from ulcer. Other narcotics administered were codeine, dihydromorphinone hydrochloride, pantopon® (a mixture of the opium alkaloids), meperidine hydrochloride, (demerol hydrochloride®) and Schlesinger's solution (scopolamine hydrobromide, 0.0025; morphine hydrochloride, 0.2; ethylmorphine hydrochloride, 0.4; distilled water, 10). Some caution regarding the use of morphine has been suggested because of its tendency to excite nausea and vomiting and because of its possible harmful effect on an anemic and anoxic respiratory center. However, other investigators have found that it puts the stomach at rest and inhibits gastric secretion. There is ample, experimental evidence to show that atropine sulfate when given generously in conjunction with morphine enhances the inhibition of gastric secretion as well as causes a reduction in the amount of free acid. The liberal use of milder sedatives such as the barbiturates often proves satisfactory in allaying anxiety and restlessness.

Diet: Dietary regimens for ulcer and for hemorrhage from ulcer have varied considerably during the course of the past twenty years. Prior to 1934, or shortly thereafter, it was the customary routine at the Johns Hopkins Hospital to place all patients with actively bleeding ulcers on a program of starvation. The experience of Meulengracht and the influence of his results from the prompt feeding regimen have resulted in a decided reversal of medical practice. Although a brief initial period of starvation still remains a common procedure among the members of the more conservative school, the fundamental principle of prompt and frequent feedings now seems to be the rule. It is generally conceded that the orthodox program of prolonged starvation failed to put the stomach at physiologic rest.

The prompt feeding program of Meulengracht offers the patient a diet adequate in calories and vitamins and rich in essental proteins. Frequent feedings administered promptly is the essential element of treatment. As suggested originally by Meulengracht and elaborated on by Rasberry and Miller, the specific type of diet or of antacid medi-

cation is really of secondary importance. Frequent feedings not only aid the patient's nutritional state, reduce free gastric acidity and motility but also bolster his morale and hasten his recovery. The harmful effects of deprivation of food and fluid on a patient bordering on peripheral circulatory failure due to hemorrhage are particularly well shown in table 6. Among 11 patients with hemorrhage from ulcer who were placed on a prolonged and strict program of starvation there were 6 deaths, or a mortality rate of 54 per cent. When contrasted with 76 patients promptly fed a modified Meulengracht diet (six feedings daily of a protein-fortified diet which is low in cellulose), among whom there were no deaths, the results are noteworthy.

TABLE 6.—*Medical Treatment*

	Number	Deaths	Per Cent Mortality
Antacid regimen (Sippy or aluminum hydroxide)..	45	5	11
Starvation	11	6	54
Meulengracht diet	76	0	0
Andresen diet	4	1	25
Total	136	12	8.8

TABLE 7.—*Value of Transfusions* *

	Number	Deaths	Per Cent Mortality
Plasma	7	1	14.3
Blood (more than 1,000 cc.)	75	6	8.0
Blood (less than 1,000 cc.)	47	4	8.5
None	90	5	5.5

* It is difficult to appraise the value of transfusions by statistical means. Individual case histories make it evident that whole blood and plasma were invaluable in combating shock and restoring blood volume.

In the original Meulengracht diet, iron medication and antacid-antispasmodic agents supplement the diet. In the present series aluminum hydroxide has been the recent antacid of choice. In table 6 the 45 patients who were treated under the antacid regimen usually had an initial period of starvation prior to the onset of a Sippy or soft diet.

An observer in Meulengracht's clinic has been quoted as saying: "The patient is urged to wipe the blood off his lips and eat a beef-steak." The value of this advice given more than ten years ago in the light of our present knowledge of protein requirements and hypoproteinemia is almost prophetic.

Transfusion: More than 50 per cent of the 218 patients in this series (table 7) received either blood or plasma transfusions. The amount of the transfusion varied from a single unit of 250 cc. to thirty-

four transfusions of 500 cc. or more of whole blood each received by a patient during the course of a single stay in the hospital. This patient subsequently underwent a subdiaphragmatic vagotomy in conjunction with a subtotal gastric resection and has had no further hemorrhage (six months after his discharge from the hospital). In this case transfusion must be surely considered the sole factor responsible for the preservation of life during the course of active hemorrhage from an ulcer.

The medical literature seems almost completely in disaccord regarding the pros and cons of transfusion as a procedure of choice in the treatment of hemorrhage from an ulcer. Those opposed to transfusion cite the statistics of Christiansen and Cullinan and Price showing an increased mortality rate following its use. On the other hand, Gordon-Taylor, in his enthusiasm, quotes Bennett as saying that "blood transfusion correctly applied is the most important single factor in saving life in gastro-duodenal hemorrhage."

From the present statistics it is difficult to appraise the value of transfusion or predicate its salutary effect on the mortality rate, for transfusions were used chiefly in the more seriously ill patients. However, from a review of the individual case histories one is impressed by the fact that whole blood and plasma were almost invaluable in combating shock and restoring normal blood volume in a number of patients seriously ill from hemorrhage.

Antacids and Other Methods of Medical Treatment: Over the course of the years spanned by this study the patients at the Johns Hopkins Hospital have received both soluble and nonabsorbable antacids. The former are represented by the salts of sodium, calcium, bismuth and magnesium and are used chiefly in the Sippy and related rituals. The nonabsorbable antacids are mainly those represented by colloidal aluminum hydroxide.

Other methods of treatment, such as the oral administration of mucin or the hyperalimentation of amino acids or hydrolyzed proteins as suggested by Co Tui were not routinely used at this hospital. Treatment by continuous intragastric drip, the insufflation of powdered posterior pituitary injection, high voltage roentgen therapy, the administration of vitamins C or K or of newer preparations such as enterogastrone, anthelone or the powdered plastic amberlite, the use of oxalic acid as a powerful blood coagulant and the ingestion of hemostatic sponges all have their proponents in the medical press, but none of these methods received a therapeutic trial in this series of cases of bleeding peptic ulcer.

Surgical Treatment.—Regardless of the perseverance of certain internists in conservative medical management of hemorrhage from an ulcer, it is a positive fact that a minimum of 5 or 10 per cent of patients

so treated die. Heuer expressed the belief that the prospects are even grimmer and stated that "approximately 15 per cent of patients who enter the hospital with massive hemorrhage die unless they can be saved by prompt surgery." Other distinguished surgeons, such as Wangensteen and Allen in this country and Gordon-Taylor and Finsterer abroad, have stated the opinion that some of these lives may be salvaged by early surgical treatment. The *British Medical Journal,* however, indicated its opinion of prompt surgical intervention during active hemorrhage from ulcer by saying:

> The subject is a debatable one, but in the absence of any really trustworthy guide to prognosis at an early stage (after which the information becomes less and less valuable) most surgeons are likely to maintain the attitude that it is not justifiable to endanger the safety of many in the hope of saving a few.

The clinical problem of the surgical care of hemorrhage from an ulcer thus resolves itself into (1) the differentiation, if possible, of cases which cannot be controlled without surgical treatment, (2) the selection

TABLE 8.—*Surgical Treatment of Bleeding Ulcer at the Johns Hopkins Hospital*

Time of operation following initial onset of bleeding	Number
1. Immediate (operation within first 48 hours)	3
2. Early (operation 3rd to 8th day)	12
3. Late (operation after 8th day with continued bleeding)	25
4. Late (operation after 8th day without continued bleeding)	42
Source of bleeding removed at operation	
1. Yes	33
2. No	49
Recurrence after operation as noted in hospital record	
1. Yes	12
2. No	12
3. Unknown	58

of an optimum time for operation and (3) the determination of which type of operation will best control the source of bleeding, save the greatest number of lives and prevent further recurrent hemorrhage. It is beyond the scope of this paper to attempt to discuss in detail the many varied solutions which have been put forth. Suffice it to say, however, that with the present limited means of prognosis there is no way of telling which cases will prove fatal if unchecked by surgical measures. Of all the criteria assembled to differentiate those who will succumb without the unctions of surgical treatment, perhaps failure of hemorrhage to stop during a medical regimen (including transfusions and prompt feeding) is the most indicative. This, of course, requires a certain time lag during which the optimal periods for early surgical intervention will have passed—the so-called golden forty-eight hours of Finsterer.

Surgical treatment of hemorrhage due to ulcer at the Johns Hopkins Hospital (table 8) has consisted for the most part of conservative management during the phase of active bleeding. Partial gastric resec-

tion (table 9) was the operation of choice in 56 patients of a total of 82 receiving surgical treatment. However, early operation in the midst of hemorrhage as suggested by Finsterer, Gordon-Taylor, Heuer, Allen and Wangensteen was infrequently performed. Late operation, usually carried out when bleeding had ceased or at least decreased its tempo, was performed in 82 per cent of the patients.

By a careful scrutiny of the operative records, the pathologic reports and the findings at autopsy, it was noted that in only 40 per cent of the operative cases was the source of bleeding actually removed by operative means. What spell of the surgical procedure caused the bleeding to cease in the remainder of the cases, in which the ulcer was left in situ, remains open to speculation. However, the hemostatic effects may be more apparent than real, for in the majority of these cases surgical intervention was delayed until the bleeding had already stopped of its own accord.

TABLE 9.—*Surgical Treatment* *

	Number	Deaths	Per Cent Mortality
Gastric resection, partial	56	4	7.1
Gastric resection, complete	0	0	0
Gastroenterostomy with excision of ulcer	7	0	0
Gastroenterostomy without excision of ulcer	6	0	0
Gastroduodenostomy	2	0	0
Vagotomy plus additional procedures	7	0	0
Miscellaneous procedures	4	0	0
Total	82	4	4.9

* The exceptionally low surgical mortality rate must be considered in the light of the somewhat higher medical mortality rate. Under a conservative surgical regimen patients considered to have severe hemorrhage are frequently too ill to undergo operation.

Follow-up notes and readmission records were available for only about one third of the patients receiving surgical treatment. A review of this limited number of follow-up cases reveals that a recurrence of hemorrhage was present about as often as not after ventriculus operations. The type of operation appeared to have little bearing on the recurrence rate. In fact the source of hemorrhage was presumed to have been removed in 7 of the 12 patients in whom hemorrhage recurred after operation.

Seven patients were subjected to vagotomy in addition to some ancillary operative procedure on the stomach, and after six months of careful follow-up study none of these had had a recurrent hemorrhage due to ulcer. This confirms a personal communication from Dragstedt in which he stated that vagotomy alone sufficed as a sovereign remedy for 34 of 35 cases of severe hemorrhage due to ulcer. No deaths

occurred, and there were no recurrences of hemorrhage in his series, although the period of follow-up was not stated.

MORBID ANATOMY

In this series there were 16 fatal cases, an over-all mortality rate of 7.3 per cent. Permission to perform an autopsy was granted in 14 of these 16 cases. In almost all the gross specimens at autopsy it was possible to demonstrate an eroded artery on the posterior wall of the duodenum or along the lesser curvature of the stomach. Bleeding ulcers astride the lesser curvature of the stomach had usually eroded into one of the major branches of the right or left gastric arteries, whereas the deep penetrating ulcers of the posterior duodenum were in the neighborhood of the pancreaticoduodenal artery and had caused necrosis of its vessel wall.

TABLE 10.—*Mortality from Medical Treatment*

	No. of Cases	Deaths	
		Number	Per Cent
Crohn, B. B.	94	4	4.2
Aitken, R. S.	234	20	8.5
Meulengracht, E.	368	5	1.3
Witts, L. J.	20	0	0
Kirsner, J. B. and Palmer, W. L.	230	7	3.1
Heuer, G. J.	306	18	5.8
Rasberry, E. A., Jr. and Miller, G. T. (collected cases)	2,111	85	4.0
Johns Hopkins Hospital	136	12	8.8
Total	3,499	151	4.3

COLLECTED STATISTICS

Data collected from the literature are difficult to appraise because they are not always clear as to the exact type of medical regimen instituted or the precise severity of the hemorrhage due to ulcer which the authors are analyzing. Complementary therapeutic procedures such as the use of transfusions, sedatives, fluids and antacids all tend to muddle the reckoning and garble the statistics. There is substantial evidence, however, to support the contention of Andresen and Meulengracht, among others (table 10), favoring prompt and frequent feeding regardless of whether a gelatin, Sippy or high protein diet be used. However, if this be the procedure of choice, surgical treatment must wait. It could be undertaken only after a few days of a conservative therapeutic trial of medical management and notwithstanding the fact that hemorrhage from ulcer has been persistent and perhaps profuse. Under such adverse conditions the operative mortality necessarily may be high, but possibly a few additional lives may be salvaged.

The fact that at this hospital the mortality of patients treated medically was 8.8 per cent among patients on a conservative regimen may be interpreted as meaning that most patients with profound exsanguination were kept on medical therapy and not subjected to surgical treatment despite their precarious condition.

The mortality from hemorrhage due to ulcer at a few of the leading surgical clinics throughout the world (table 11) reveals a wide range of death's roll call. Finsterer advocated immediate surgical intervention within the early stages of active hemorrhage. The mortality in his skilful hands was only 5.9 per cent. In the period between 1933 and 1939 Gordon-Taylor found an operative mortality of 5.5 per cent among personal cases in which he operated early. Patients who were operated on late had a fatality rate of 36 per cent. At the Johns Hopkins Hos-

TABLE 11.—*Mortality from Surgical Treatment*

	No. of Cases	Deaths	
		Number	Per Cent
Crohn, B. B.	7	5	71.4
Ross, K.	43	26	60.4
Aitken, R. S.	21	7	33.3
Finsterer, H.	51	3	5.9
Allen, A. W.	144	21	14.6
Heuer, G. J.	31	9	29.0
Gordon-Taylor, G.	71	13	18.3
Wangensteen, O. H.	10	2	20.0
Johns Hopkins Hospital	82	4	4.9
Total	460	90	19.5

pital the patients were for the most part operated on late; the mortality rate of 4.9 per cent is a creditable record regardless of the favorable cases chosen.

SUMMARY

A study of 218 cases of bleeding peptic ulcer is presented. All patients in this series had gross hemorrhage due to ulcer and were treated as bed patients at the Johns Hopkins Hospital.

The statistics of this group of cases were analyzed according to yearly and monthly incidence and race and sex ratios. The morbidity was reviewed as related to age, loss of blood, arteriosclerosis, gastric retention, azotemia, intractable pain, number of episodes of bleeding and history of ulcer. The selection of patients whose hemorrhage is likely to prove fatal if not surgically checked as contrasted with those whose hemorrhage is likely to cease spontaneously remains primarily a problem of clinical judgment.

All aspects of the medical treatment of hemorrhage from ulcer are considered, and the value of a prompt and frequent feeding program is

emphasized. A modified Meulengracht regimen combined with antacids and transfusions resulted in no deaths in 76 cases.

The surgical treatment of 82 patients with bleeding ulcer is analyzed with respect to time of operation, surgical procedure, operative attack on the source of bleeding and recurrence rate. The value of vagotomy in 7 patients with hemorrhage due to ulcer is discussed.

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EFFECT OF APPLICATION OF SEVERAL ANTIBACTERIAL SUBSTANCES ON HEALING OF WOUNDS

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DETROIT

IN SEVERAL previous communications from this laboratory,[1] there have been presented the results of simple animal experiments to determine the effect of the topical application of various agents on the healing of wounds. We have observed the healing of two symmetric cutaneous defects on the abdominal wall of the guinea pig; one of these wounds was treated with the test substance while the other served as a control. This type of experiment appears to be a reliable indicator of the response which may be expected from human tissue. For example, a number of substances recommended for the treatment of burns were tested.[1b] Among these was tannic acid, which produced a conspicuous delay in healing. This experimental finding has had ample clinical confirmation. Many other agents have failed to show the stimulating effect claimed by their sponsors. This paper presents the results of experiments on wound healing with five antibacterial substances which have been used more or less extensively in local treatment: sulfanilamide, sulfathiazole, sulfadiazine, penicillin and nitrofurazone (furacin,® 5-nitro-2-furaldehyde semicarbazone).

Although the sulfonamide compounds have been employed widely, there are surprisingly few reports of controlled healing experiments with them. Bricker and Graham [2] stated that they could detect an inhibitory effect on the tensile strength of healing stomach wounds when their dogs were fed 3 Gm. of sulfanilamide daily. Taffel and Harvey [3] carried out

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1. (*a*) Brush, B. E., and Lam, C. R.: The Effect of the Topical Application of Several Substances on the Healing of Experimental Cutaneous Wounds, Surgery **12**: 355, 1942. (*b*) Brush, B. E.; Lam, C. R., and Ponka, J. L.: Wound Healing Studies on Several Substances Recommended for the Treatment of Burns, ibid. **21**:662, 1947. (*c*) Cowley, L. L. and Brush, B. E.: Tantalum Oxide and Wound Healing, Proc. Soc. Exper. Biol. & Med. **65**:60, 1947. (*d*) Lam, C. R., and Brush, B. E.: Chlorophyll and Wound Healing: Experimental and Clinical Study, Am. J. Surg., to be published.

2. Bricker, E. M., and Graham, E. A.: The Inhibitory Effect of Sulfanilamide on Wound Healing, J. A. M. A. **112**:2593 (June 24) 1939.

3. Taffel, M., and Harvey, S. C.: Effect of Sulfanilamide on Wound Healing, Proc. Soc. Exper. Biol. & Med. **45**:647, 1940.

similar experiments with rats but did not note a similar effect. Smith and Livingston,[4] using a variety of animals, found delay in healing of 60 per cent of the wounds treated with sulfanilamide powder. With sulfathiazole and sulfadiazine, the delay in healing was observed in 50 and 40 per cent of the animals, respectively.

A controlled clinical study was carried out by Bick,[5] who placed sulfonamide drugs in 50 clean operative wounds and compared the healing with that of 50 controls. He found that healing was retarded at least 50 per cent and that there was excessive cutaneous scarring. A diametrically opposed opinion was expressed by Key,[6] who implanted the drugs in more than 600 operative wounds. The local complications in this series included 7 hematomas, 1 separation of wound margins, 2 stitch abscesses and 2 infections. It was thought that the remaining wounds healed in a normal manner without excessive scar formation and that the average period of hospitalization was shortened by the use of the drugs.

Posch, Maun, Pilling and Hirshfeld[7] put sulfanilamide and sulfathiazole crystals into the subcutaneous tissues of human volunteers and removed the entire wounds for microscopic study after varying intervals of time. They concluded:

> From a study of the excised biopsy specimens it is evident that sulfanilamide and sulfathiazole act as irritants to the dermis and the subcutis. In addition, they may produce necrosis and marked leucocytic response in adjacent tissues. However, the deleterious effects are short-lived and are not evident in wounds 7 to 10 days old.

Studies of the Subcommittee on Surgical Infections of the National Research Council, published by Meleney,[8] indicated that the sulfonamide compounds did not lessen the incidence of local infection in contaminated wounds, compound fractures or burns.

Howes[9] reported the toxicity of a number of antibacterial substances for tissue cultures of epithelial cells. Benzalkonium chloride (zephiran

4. Smith, L. W., and Livingston, A. E.: Chlorophyll: An Experimental Study of Its Water Soluble Derivatives in Wound Healing, Am. J. Surg. **62**:358, 1943.

5. Bick, E. M.: Observations on the Topical Use of Sulfonamide Derivatives, J. A. M. A. **118**:511 (Feb. 14) 1942.

6. Key, J. A.: Wound Healing and Infection After Local Implantation of Sulfonamide Powder, J. A. M. A. **122**:1003 (Aug. 7) 1943.

7. Posch, J. L.; Maun, M. E.; Pilling, M. A., and Hirshfeld, J. W.: The Effect of Sulfanilamide and Sulfathiazole on Human Tissue, Surg., Gynec. & Obst. **80**:143, 1945.

8. Meleney, F. L.: The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, Ann. Surg. **118**:171, 1943.

9. Howes, E. L.: Local Chemotherapy of Wounds, Surg., Gynec. & Obst. **83**:1, 1946.

chloride®), P-chlorophenol and tyrothricin in the dilutions employed to inhibit the growth of bacteria were toxic to the cells. Penicillin calcium was inert, while streptomycin and sulfamylon® (para-[aminomethyl]-benzene sulfonamide) were mildly inhibitory. Wound-healing studies on nitrofurazone were carried out by Dodd, Hartmann and Ward.[10] They found that it did not delay the healing process in rabbits.

PRESENT STUDY

Method.—The guinea pig was anesthetized with ether, and the abdomen was shaved and prepared with an antiseptic solution (hexylchloro-m-cresol). Symmetric circular or ovoid cutaneous defects were made on each side of the midline (fig. 1). The wound on the animal's left served as the test wound, and the other

Fig. 1.—Freshly made cutaneous wounds on the abdominal wall of a guinea pig.

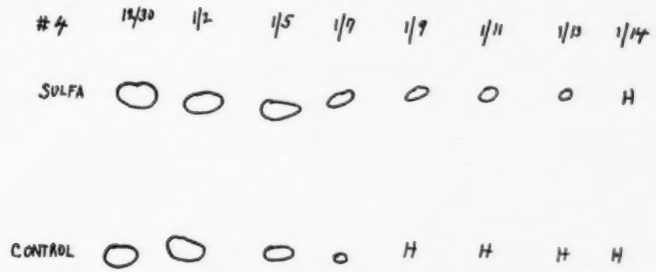

Fig. 2.—Tracings showing progress of a typical experiment (application of sulfanilamide crystals to a test wound).

was the control. After recording the original size of the wounds by tracing the outlines on sterile cellophane, we applied the test substance to the appropriate wound. The control wound was covered with petrolatum gauze. Ordinary gauze squares completed the dressing on both wounds. The dressing was held in place by a 3 inch (7.61 cm.) wide strip of adhesive tape passed around the animal's body. The wounds were measured every two days, at which time more of the test substance was applied. Each agent was used on 12 animals.

10. Dodd, M. C.; Hartmann, F. W., and Ward, W. C.: The Local Application of Nitrofuran Compounds with Special Reference to Use on Wounds, Surg., Gynec. & Obst. **83**:73, 1946.

The sulfonamide compounds were used in the form of sterile, dry crystals. The wounds were liberally frosted. The penicillin was in the form of an oxycholesterol-petrolatum ointment base (aquaphor®) containing 1,000 Oxford units per gram. The nitrofurazone (furacin®) was in a base consisting of carbowax 1540,® [11] carbowax 4000® and polyethylene glycol (furacin-soluble dressing®).

Results.—Figure 2 is a sample of the type of permanent record made by transferring the cellophane tracings to white paper. Results of a

TABLE 1.—*Effect of Sulfanilamide Crystals on Experimental Wound Healing*

Animal No.	Days Required for Healing		Effect on Healing*
	Control Wound	Test Wound	
1	13	15	Delayed
2	11	16	Delayed
3	11	15	Delayed
4	11	16	Delayed
5	Died seventh day		..
6	Died fifth day		..
7	11	13	Delayed
8	11	13	Delayed
9	11	13	Delayed
10	13	14	Delayed
11	15	16	Delayed
12	15	15	No effect

* Healing was delayed in 9 of the 10 animals which survived. The cause of death of 2 animals is not known.

TABLE 2.—*Effect of Nitrofurazone (Furacin®) on Wound Healing*

Animal No.	Days Required for Healing		Effect on Healing*
	Control Wound	Test Wound	
1	12	14	Delayed
2	12	10	Hastened
3	10	10	No effect
4	12	12	No effect
5	10	10	No effect
6	13	12	Hastened
7	10	10	No effect
8	12	13	Delayed
9	17	14	Hastened
10	12	12	No effect
11	12	12	No effect
12	14	14	No effect

* The drug had no effect in 7 animals, delayed healing in 2 animals and accelerated healing in 3 animals.

typical experiment, consisting in the application of sulfanilamide crystals to wounds on 12 animals, are represented in table 1. It is seen that in no instance did the wound treated with the crystals do better than the control, and in 9 of the 10 animals which survived there was delay in

11. Carbowax compounds are polyethylene glycols of high molecular weight.

healing on the treated side. From these facts it is concluded that the drug is inhibitory, and this effect is indicated in the conclusions in table 3. The data on another typical experiment are presented in table 2. It is evident that there was no significant acceleration or delay in wound healing as a result of the application of nitrofurazone (fig. 3).

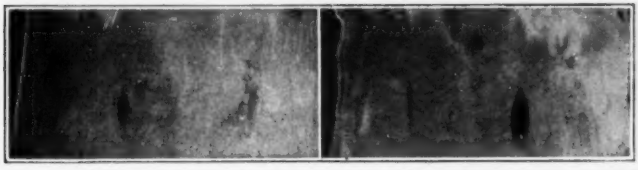

Fig. 3.—Wounds on 2 animals from the sulfadiazine series. (*A*) Both wounds healed on the eleventh day. (B) The control wound healed; the wound treated with sulfadiazine did not heal until four days later.

TABLE 3.—*Summary of Experiments on Effect of Five Antibacterial Substances on Wound Healing*

Substance Tested	Healing Hastened	No Effect	Healing Delayed	Conclusions of Effect on Healing
Sulfanilamide	0	1	9	Delays
Sulfathiazole	2	3	7	Delays
Sulfadiazine	3	7	2	No effect
Penicillin	3	6	3	No effect
Nitrofurazone ("furacin")	3	7	2	No effect

SUMMARY

Five antibacterial substances were placed on uninfected wounds in guinea pigs to determine the effect on the rate of healing. Sulfanilamide and sulfathiazole crystals caused delay in healing. The wounds dressed with sulfadiazine, penicillin ointment and nitrofurazone (furacin®) healed in the same time as did the controls.

COSTOCLAVICULAR COMPRESSION

Relation to the Scalenus Anticus and Cervical Rib Syndromes

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THIS study includes a series of cases in which the subclavian artery and brachial plexus were compressed between the clavicle and the first rib. In a previous paper [1] a series of 9 cases of cervical rib were reported, in 5 of which costoclavicular compression of the neurovascular structures leading to the arm was the outstanding feature. In the present series of 14 cases a cervical rib was actually present in only 2. In the remaining 12 the compression was between the clavicle and the first thoracic rib. The condition is characterized by vascular and neurologic symptoms together or separately. The pulse to the arm is markedly reduced in volume or shut off entirely when the shoulders are thrown back as in the attention position.

On reviewing the literature, one finds many theories formulated in an attempt to explain the mechanism producing symptoms in the so-called scalenus anticus and cervical rib syndromes. Yet these theories do not explain adequately the circulatory disturbances often found. The scalenus anticus muscle as an instrument of counterpressure has enjoyed considerable popularity.[2] Irritation of abnormally placed sympathetic nerve fibers as they cross a cervical or first thoracic rib has been considered a factor in vasospasm.[3] The clavicle, except in a few recent

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1. McGowan, J. M.: Cervical Rib: The Role of the Clavicle in Occlusion of the Subclavian Artery, Ann. Surg. **124**:71-88 (July) 1946.

2. Adson, A. W., and Coffey, J. R.: Cervical Rib: Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus, Ann. Surg. **85**:839-857 (June) 1927.

3. (*a*) Blair, D. M.; Davies, F., and McKissock, W.: The Etiology of the Vascular Symptoms of the Cervical Rib, Brit. J. Surg. **22**:406-414 (Jan.) 1935. (*b*) Jones, F. W.: Discussion on Cervical Rib, Lancet **1**:609-611 (March 1) 1913. (*c*) Telford, E. D., and Stopford, J. S. B.: The Vascular Complication of the Cervical Rib, Brit. J. Surg. **18**:557-564 (April) 1931. (*d*) Todd, T. W.: Indications of Nerve Lesions in Certain Pathological Conditions of Blood Vessels, Lancet **1**:1371-1372 (May 17) 1913.

contributions, has not been given the place it warrants as a factor of counterpressure in these compression syndromes.[4]

Adson and Coffey[2] in 1928 attempted to show that symptoms occurring in cases of cervical rib were often due to pressure from the scalenus anticus muscle. They claimed relief of symptoms by scaleniotomy without removal of the anomalous rib. They devised a test later referred to as the Adson maneuver which was believed to indicate whether or not the scalenus anticus muscle was producing neurovascular compression in a case of a cervical rib. This test consists of turning the head to the side of the lesion, hyperextending the neck and taking a deep breath. The scalenus anticus muscle presumably would then be put under sufficient tension to compress the subclavian artery decreasing or shutting off the pulse to the arm. Actually, the scalenus anticus muscle itself should not increase in tension on the affected side in this maneuver but should reciprocally relax unless it happened to be the site of fibrosis, as will be seen later is frequently the case.

Ochsner, Gage and DeBakey[5] reported a series of cases without cervical rib in which they believed abnormal compression to the neurovascular structures passing to the arm was produced by the scalenus anticus muscle. In these cases they found a fibrositis of the offending muscle. They believed that the fibrositis led to spasm of the muscle elevating the first rib, which resulted in compression and stretching of the large nerve trunks. It was their belief that this condition frequently occurred in persons in whom the shoulder descended to an abnormally low level. Actually, compression symptoms from the descent of the shoulder would not be expected to be produced by the scalenus anticus muscle, which is not attached to the shoulder girdle. It is highly probable that the compression of the subclavian artery in the Adson maneuver and the fibrosis of the scalenus anticus as found by Ochsner were often both due to pressure from the clavicle.

Craig and Knepper[6] suggested that scaleniotomy alone is not sufficient in many cases and recommended the removal of the cervical rib in addition.

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4. (*a*) Aynesworth, K. H.: The Cervicobrachial Syndrome: A Discussion of the Etiology: Report of Twenty Cases, Ann. Surg. **111**:724-742 (May) 1940. (*b*) Falconer, M. A., and Weddell, G.: Costoclavicular Compression of the Subclavian Artery and Vein, Lancet **2**:539-543 (Oct. 30) 1943. (*c*) Walshe, H. J., and Wayburn-Mason, R.: Pressure Effects Associated with Cervical, Rudimentary, and Normal First Ribs: Factors Entering Into Causation, Brain **67**:141-177 (Sept.) 1944. (*d*) Wright, I. S.: The Neurovascular Syndrome Produced by Hyperabduction of the Arms, Am. Heart J. **29**:1-19 (Jan.) 1945.

5. Ochsner, A.; Gage, M. T., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, Ann. Surg. **28**:669-672 (June) 1935.

6. Craig, W. M., and Knepper, P. W.: Cervical Rib and Scalenus Anticus Syndrome, Ann. Surg. **105**:556-563 (April) 1937.

Telford,[3c] Todd,[3d] Jones [3b] and Blair [3a] believed that the circulatory disturbances associated with cervical rib syndrome were due to irritation of the sympathetic nerve fibers as they passed over the anomalous rib.

Neither the scalene compression theory nor the theory of irritation of the sympathetic nerve fibers adequately explains many factors, among which are (1) the frequent occurrence of an aneurysm in the subclavian artery just beyond the scalenus anticus muscle and (2) embolic phenomena which may occlude any of the smaller peripheral arteries singly. These conditions are best explained on the basis of costoclavicular compression.

Falconer and Weddell [4b] reported 3 cases in which the subclavian artery was compressed between the clavicle and the first thoracic rib. In these cases the pulse was obliterated when the shoulders were thrown down and back. They were able to demonstrate compression of the subclavian artery between the clavicle and the first rib on the operating table before and after scaleniotomy. In the same case they were able to demonstrate absence of scalene compression by the Adson maneuver performed at the operating table with the scalenus anticus muscle exposed. They tested 100 apparently normal persons by having them throw the shoulders down and back and found that the pulse was reduced in volume in 54 cases. They must have caused their subjects to force the shoulders down and back to a considerable degree because in a larger series of apparently normal persons we were not able to cause the same degree of pulse occlusion as in the cases presenting costoclavicular compression symptoms.

Among others who recognized the importance of the clavicle in these compression syndromes are Walshe and Wayburn-Mason.[4c] It was their impression also that the compression symptoms are due to the pressure between the clavicle and the first thoracic or cervical rib. The findings reported in this paper are in agreement with the observations of the authors who state: "The clavicle and first rib act like the two arms of a vise in which the intervening structures are recurrently compressed."

This theory does not exclude the role of the first thoracic rib in traction, stretching and angulation. The damage to the artery as a result of excessive exercising leads to thrombosis in the wall. Thrombi are then broken off and produce emboli in smaller vessels, leading to ischemia and even gangrene. Intermittent compression involves the arteries, muscles and nerves. The cause of the symptoms is related to (1) the respiratory excursions of the thoracic cage which occurs 23,000 times in twenty-four hours and (2) the movements of the shoulder. The recurrent friction, stretching and compression sets up an inflammatory reaction around the structures between the rib and the clavicle.

Stretching alone may affect the lower trunk of the brachial plexus, producing symptoms referable to the ulnar nerve.

One of the cases which one of us (McGowan) previously reported [1] presented a picture similar to that just mentioned. The patient had thrombosis in the right radial and ulnar arteries, with beginning gangrene in three fingers. It was found that his brachial pulse was obliterated when he threw the shoulders back as in the position of attention. This occlusion was found to be between the clavicle and a cervical rib and was not related to the scalenus anticus muscle. Proof of this was furnished by the fact that the pulse could be felt in the posterior triangle of the neck beyond the scalenus anticus muscle at the same time that it could not be felt in the brachial artery. In 3 cases previously reported in this same paper in which the pulse was occluded in the attention position, a process of fibrosis involving the muscles, arteries and nerves was found at operation.

Hansson [7] has recommended exercises in cases of scalenus anticus syndrome aimed at elevation of the shoulder girdle by strengthening the trapezius and levator scapulae muscles. Favorable results reported from such exercises are an indication that the clavicle must have been the important factor of counterpressure since elevation of the shoulder would not have affected the scalenus anticus muscle.

Judovich and others [8] and Aynesworth [4a] have separately mentioned the importance of narrowing of the costoclavicular space in cervical rib and scalenus anticus syndromes.

CLINICAL ASPECTS

The important etiologic factor in this compression syndrome is, therefore, a narrowing of the space between the clavicle and the first thoracic or cervical rib. The structures in this costoclavicular space, as previously mentioned, are compressed by a vise, one arm of which is formed by the clavicle and the other by the first rib. This is part of the price which some human beings must pay for the privilege of walking in the upright position, for if man walked on all fours or swung from a tree, the clavicle would be thrust forward, leaving an adequate costoclavicular space for the arterial and nerve trunks to pass to the extremity concerned.

A factor leading to the narrowing of the costoclavicular space may be abnormal descent of the shoulder girdle such as occurs in persons with muscular weakness, particularly in the aged. It may also occur in a soldier from carrying a pack or a rifle. A second factor which narrows

7. Hansson, K. G.: Scalenus Anticus Syndrome, S. Clin. North America **22**:611-620 (April) 1942.

8. Judovich, B.; Bates, W., and Drayton, W., Jr.: Pain in the Shoulder and Upper Extremity Due to Scalenus Anticus Syndrome, Am. J. Surg. **63**:377-381 (March) 1944.

the costoclavicular space is the abnormal elevation of the first rib. This may be brought about by excessive use of the muscles of extraordinary respiration, particularly those of the scalene group, such as occurs in vigorous exercises associated with basic military training or in persons suffering from emphysema. The intermittent compression sets up an aseptic inflammatory reaction leading to fibrosis involving the scalenus anticus muscle, the subclavian artery and the trunks of the brachial plexus. This reaction may spread to involve even the stellate ganglions, gradually producing a sympathetic disturbance which is irritative at first and leads to vascular spasm and later is paralytic and results in Horner's syndrome.[4c]

Symptoms may be neurologic or vascular or both. Neurologic symptoms consist of pain in the scapular region radiating up the back of the neck and down the arm. This pain is of a lancinating character and may be aggravated by depression of the shoulder, pressure lateral to the scalenus anticus muscle or abnormal positions such as that of the Adson maneuver or the position of attention.

Physical examination may reveal paresthesia or anesthesia of the area supplied by the ulna nerve, although frequently the median nerve may be involved. Trophic disturbances such as muscular atrophy, absence of hair, weakness of the grip or deformities of the nails may occur.

The vascular symptoms are manifested by numbness of the extremities and pallor coming on during periods of downward and backward depression of the shoulders such as occurs in carrying a pack or rifle or in standing at attention for a long period.

Diagnosis is made by having the patient throw the shoulders down and back as in the attention position. The pulse will be reduced in volume or completely obliterated. A positive reaction to the Adson maneuver indicates that the scalenus anticus muscle is the seat of fibrosis and division of this muscle should result in a cure.

Treatment consists of exercises aimed at strengthening the trapezius and levator scapulae muscles, and so producing elevation of the shoulder. The patient is instructed not to throw his shoulders back in assuming the position of attention but to allow them to hang freely or even to drop slightly forward. Removal of a part of the first rib has been done by Falconer and Weddell. Removal of the clavicle has not been performed for this condition but has been done with impunity for other conditions and without weakening the shoulder girdle. It seems that removal of the middle third of the clavicle might be beneficial in severe cases not responding to exercises.

METHOD OF STUDY AND FINDINGS

One hundred and twenty-nine persons were studied with reference to this syndrome. Of these, 108 were supposedly normal recruits who were checked during their routine physical examination for officer candi-

date school. These showed no abnormal symptoms. The remaining 21 presented themselves with symptoms referable to the arm simulating the scalenus anticus or cervical rib syndrome. Of these, 14 were definitely found to have costoclavicular compression. The symptoms were either vascular or neurologic. The vascular symptoms included swelling in the arm, numbness of the arm when at the attention position especially while wearing a heavy overcoat, numbness while driving a truck or carrying a pack, pallor and coldness of the extremity. The neurologic symptoms complained of included muscle weakness in the hand and arm, pain in the shoulder, a tingling sensation, muscle atrophy, pain over the scapula radiating down the medial aspect of the arm aggravated by pressure over the scalenus anticus, pain in the pectoral region aggravated by turning the head, tingling, hyperesthesia, pain in the scapular region radiating up the back of the neck and numbness in the arm following weight bearing. Blood pressure determinations were made on each arm with the patient standing, under the following conditions: (1) with the shoulders in the normal forward position; (2) with the head turned toward the affected side and hyperextended as in the Adson maneuver, and (3) with the shoulders pressed down and back in the attention position.

Of the 14 patients with costoclavicular compression, 7 had symptoms on the right side, 5 had symptoms on the left and 2 had symptoms on both sides. Eleven of these men were right handed, and 3 were left handed so far as writing was concerned; however, 3 right-handed patients preferred to use the left arm for most weight-bearing tasks but had been taught to use the right hand in school. Of the 6 actually left-handed persons, 5 had symptoms on that side. The sixth left-handed person preferred to use the left arm because of muscular weakness in the right, which arm remained asymptomatic until he was obliged to use it to carry a rifle or a pack. In general, therefore, symptoms occurred in the arm that was the most frequently used for weight bearing in every case except in the one in which there was muscular weakness on the opposite side. In most cases the shoulder on the symptomatic side was lower than that on the other side. In 3 cases this shoulder was lower because of faulty posture (fig. 1*A*).

The attention position produced a reduction or obliteration of the pulse on the affected side in all 14 cases and a complete obliteration of the pulse in 10 of those cases. This test is carried out in the following manner: A blood pressure cuff is placed around the upper part of the arm with the patient in a standing position. The shoulder is held well forward and upward and the blood pressure is recorded. The patient is then asked to put the shoulders down and back approximately in the position adopted by a soldier at attention. The blood pressure readings are again taken. The reaction to the test is considered positive when

there is a reduction of blood pressure of 20 points or more. In the 4 patients with incomplete obliteration of pulse the attention position resulted in a reduction of blood pressure ranging from 25 to 75 mm. of mercury. In only 3 cases were there positive findings on the unaffected side, and in these they were more pronounced on the affected side. In only 1 case was the pulse reduced equally on both sides, and in that case symptoms were bilateral. The reaction to the attention position test as an index of costoclavicular compression was found to be 100 per cent in agreement with the symptoms.

With the Adson maneuver the findings were less specific. This maneuver is carried out as follows: The blood pressure cuff is placed on

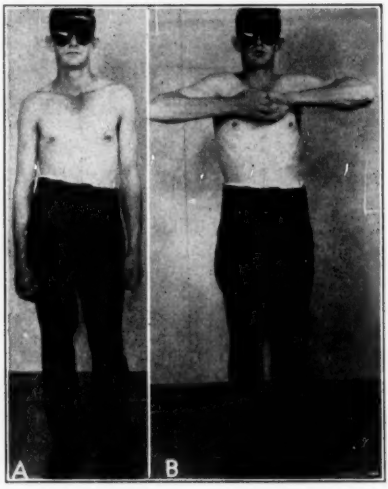

Fig. 1.—*A*, a case of costoclavicular compression from faulty posture. This is the position the man had adopted in standing before entering the army. Note the low level of the right shoulder. *B*, note the leveling effect on the shoulders of the first phase in corrective exercises. The second phase consists of bringing the hands over the head clasped in this manner.

the arm, the shoulder is placed forward and upward and the blood pressure is recorded. With the shoulder still in the forward position, the head is turned to the side being studied, and the patient is then asked to throw the head back, look up to the ceiling and take a deep breath. The reaction to the test is considered positive if there is a reduction in systolic blood pressure of 20 points or more. A positive reaction indicates fibrosis in the scalenus anticus muscle. The reaction was positive in 9 cases of the 14. The pulse was completely obliterated in only 1 case, as against 10 in the attention position test. Among the 9 cases in which the test

gave a positive reaction, vascular compression was present on both sides in 4 cases and on the affected side alone in only 5 cases. In the 14 cases studied, the Adson maneuver elicited a specifically positive reaction in only 5. There were 5 cases in which the Adson maneuver elicited a negative reaction and the attention position a positive reaction. There were 3 cases in which the Adson maneuver gave a false positive reaction, that is, when the patient assumed the position for the maneuver, he automatically pushed the shoulder down and back, so reducing the pulse volume by costoclavicular rather than by scalene compression. When the test was repeated with the shoulder kept in a forward position, the reaction was found to be negative. It is probable that many patients in the past reported as reacting positively to the Adson maneuver and with a diagnosis of the scalenus anticus syndrome, and indeed frequently operated on, actually suffered from costoclavicular compression.

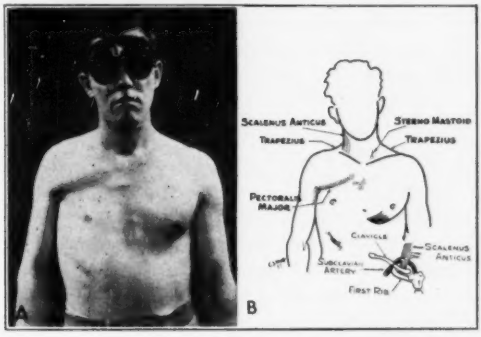

Fig. 2.—*A*, a case of costoclavicular compression as a result of lack of support to the shoulder girdle because of muscle weakness and dorsal scoliosis which elevates the first rib toward the clavicle. Note atrophy of the right major pectoral and trapezius muscles. The shoulder was supported only by the levator scapulae muscle. Note also the lack of prominence of the sternomastoid muscle on the right. The scalenus anticus muscle is unusually prominent (compensatory hypertrophy), producing further elevation of the first rib. The shoulder is held in an elevated position in order to avoid costoclavicular compression. However, 30 pounds (13.6 Kg.) of pressure on the tip of the shoulder was sufficient to depress it to the point at which the pulse was occluded. *B*, a diagrammatic key to *A*.

The ages of the 14 patients were 18 to 42 years. The length of service was less than four months in all but 3 cases. The short duration of service is explained partially by the fact that patients were drawn from an infantry replacement training center, where the period of training did not exceed three months in many cases. The 3 patients in the older age group could be explained on the basis of a weakening of the trapezius muscle resulting in a drop of the shoulder girdle. One of these patients had been in the tropics for thirty-four months, where general muscular atony had developed. The other 2 had had sedentary occupations in the army and

had suddenly been transferred to an actively training unit. Symptoms before induction were present in 7 cases, 50 per cent. The condition could have been picked up in the remaining 7 during the course of the induction examination by simply having each man throw the shoulders back at attention while the radial pulse was being palpated by the examiner.

TREATMENT

All patients were treated by having them placed on limited duty, with avoidance of weight bearing or carrying a pack or a rifle. They were instructed not to throw their shoulders down and back during the attention position but to allow them to remain slightly forward. They were instructed in exercises aimed at strengthening the trapezius and levator scapulae muscles (fig. 1*B*). The results could be evaluated properly in only 4 cases which could be followed, and in these improvement was striking. The remaining men probably were improved, because they usually returned fairly promptly from their units if they continued to have symptoms. The training in this particular camp was at a fast tempo, and men were rapidly returned to the hospital if they were unable to keep up the pace.

CONTROL STUDY

In order to evaluate the accuracy of the present findings 108 apparently normal persons were studied. These were taken from a group of men during the routine examination for admission to officer candidate school. The tests were performed before the man was questioned concerning any symptoms referable to the arm. The following tests were conducted: (1) Adson maneuver; (2) the attention position of the shoulders; (3) extreme backward and downward shoulder compression (exaggerated attention position), and (4) roentgen study for evidence of cervical rib.

The findings showed 88 patients in whom the reactions to all tests were entirely negative and who had no subjective symptoms; 16 patients showed a diminution of the pulse to the arm, particularly in the exaggerated attention position but not a complete absence of pulse beat. All these 16 men had hypertrophy of the neck musculature, but there were no subjective symptoms. The decrease of pulse beat in these 16 cases we do not consider abnormal. They correspond to the cases reported by Falconer and Weddell, who found forceful decrease in pulse volume in downward and backward shoulder compression. The remaining 4 of the 108 controls showed definite evidence of abnormality.

The first of these 4 patients presented an absence of pulse in the "position of attention," with a negative reaction to the Adson maneuver. This man had symptoms consisting of a tingling sensation and numbness in the hands while at attention and when carrying a pack. Roentgenologic examination showed bilateral cervical rib. The second patient

presented a diminution of pulse beat on both sides while in the attention position and an absence of pulse in the extreme attention position but a negative reaction to the Adson maneuver. He had no subjective symptoms except for occasional numbness of short duration. The third patient presented a positive reaction to the Adson maneuver on both sides. The radial pulse at attention position and extreme attention position was also obliterated bilaterally. This man had no subjective symptoms in spite of the fact that he had completed thirteen weeks of basic training. Roentgenologic study did not reveal a cervical rib. The fourth patient reacted negatively to all compression tests but showed bilateral cervical rib on roentgen examination. These were too short to produce symptoms.

In summary, among 108 presumably normal soldiers examined consecutively for evidence of costoclavicular compression, the reaction to the attention position test was positive in only 3. Two of these had symptoms of costoclavicular compression, and 1 had no symptoms. The attention position test, as evidence of costoclavicular compression has, therefore, an accuracy slightly better than 99 per cent.

REPORT OF CASES

CASE 1.—H. W., a white man aged 28, was first seen in May 1945. His chief complaint was pain in the right scapular region of five years' duration.

History of Present Illness.—Five years previous to his admission he suffered frequent attacks of severe pain in the right scapular region while driving a truck. In the two years preceding his induction into the army he worked in the fire department and was entirely symptom free. He entered the armed forces on Dec. 14, 1944. Shortly after beginning his training he felt pain in the right scapular region radiating down the arm while carrying a pack or rifle. The arm would frequently become numb.

Physical Examination.—This revealed the fact that the pulse to the right arm was completely obliterated when the shoulders were thrown back in the attention position. There was no such change in the blood pressure in the opposite arm. The Adson maneuver elicited a negative reaction on both sides. The following tabulation indicates the blood pressure changes with the different tests.

	Normal	Adson Maneuver	Attention Position
Right arm	128/84	124/84	0/0
Left arm	124/84	124/84	124/84

When the Adson maneuver was first performed on the right, the patient simultaneously pushed the shoulder down and back and so produced a complete obliteration of the pulse and gave a false positive reaction. However, when the test was repeated with care being taken to have the patient keep his shoulder forward, the pulse was no longer shut off.

Comment.—This is a sample of a patient with the costoclavicular syndrome with no evidence of scalenus fibrosis. A false positive reaction to the Adson test was produced when the shoulder was not kept forward. This is the type of case in which scaleniotomy could be erroneously performed, and it probably has been done in similar cases in the past.

CASE 2.—A youth aged 19 was first seen on July 19, 1945. He had entered active duty on May 29. The following is an abstract of his clinical record. His chief complaint was numbness of the right arm of five days' duration.

History of Present Illness.—One year previously he was engaged in farm work in which he would milk three to four cows by hand. After milking, he would carry two 3 gallon (11 liter) pails a distance of 110 feet (36 meters). He noticed that he would wake in the mornings with numbness in both hands. Normal sensation would return in the hands after shaking them a few minutes. He entered active duty on May 29, 1945, and on July 14 he went on a 7 mile (11,263 meter) hike with full pack. As soon as he got his pack and rifle on, the right hand and arm became numb. Previous to this time, carrying a rifle would produce temporary numbness. This particular attack, however, persisted until the time of examination five days later, although the numbness was then rapidly disappearing.

Physical Examination.—This showed that the right shoulder was considerably lower than the left. Blood pressure studies on both arms in various positions showed that the pulse beat on the right side was completely obliterated in the "attention position." The Adson maneuver produced a reduction in pulse beat on both sides. The following tabulation indicates the blood pressure readings.

	Normal	Adson Maneuver	Attention Position
Right arm	120/80	84/60	0/0
Left arm	120/80	90/80	100/90

Comment.—This patient suffered from costoclavicular compression on both sides, more so on the right. Symptoms were brought on at first by milking cows and carrying heavy pails and later by carrying a pack or rifle. The results of the Adson maneuver indicated that there was some fibrosis in both scalene muscles.

COMMENT

Among the 14 cases of costoclavicular compression studied, the Adson maneuver gave a specifically positive reaction in only 5. This indicates that in these 5 cases there was fibrosis of the scalenus anticus, probably a result of intermittent pinching of this structure between the clavicle and the first rib. The subjects were mostly all young men in whom symptoms had been present a relatively short time. It is probable that in an older age group with narrowing of the costoclavicular space a much higher incidence of fibrosis of the scalenus muscles would be present.

Compression of the subclavian artery and brachial plexus nerve trunks may occur at one of three places: (1) behind the scalenus anticus muscle; (2) between the clavicle and the first rib, and (3) beneath the pectoralis minor muscle.[4d] These three conditions are diagnosed by three separate maneuvers: (1) the Adson maneuver, (2) the shoulder attention position and (3) hyperabduction of the arm.

Patients with costoclavicular compression have probably been benefited by scaleniotomy in the past because the costoclavicular space is increased, which makes more room for the neurovascular structures. This increase in roominess is accomplished in two ways: (1) the first rib descends

when the muscle is cut, and (2) the muscle retracts, leaving one less bulky structure in the costoclavicular space.

The cases herein reported were all studied in military service. However, since resuming private practice, we have encountered 7 cases of costoclavicular compression. This leads one to believe that the condition is much more common than supposed and that it will be diagnosed more frequently as it becomes better known.

SUMMARY AND CONCLUSIONS

1. Evidence is presented to show that many symptoms attributed to the scalenus anticus muscle are actually due to costoclavicular compression. The neurovascular structures passing to the arm are intermittently compressed as in a vise the jaws of which consist of the clavicle and the cervical or first thoracic rib. This compression is readily produced by a simple test in which the pulse to the arm is markedly reduced or shut off when the shoulders are placed in the "attention position."

2. Many patients when being tested for scalenus anticus syndrome by means of the Adson maneuver will automatically push the shoulder down and back, producing occlusion of the pulse due to costoclavicular compression. This leads the examiner to believe that he is dealing with a scalenus anticus syndrome. Section of the scalenus anticus muscle may at times produce some benefit because of an increase in size of the costoclavicular space. However, the erroneous etiologic conception may account for some of the disappointing results reported.

3. Twenty-one patients complaining of vascular or neurologic disturbances of the arm were studied. Fourteen of these were found to be suffering from a costoclavicular compression syndrome. In all the pulse was reduced in volume or completely occluded when the shoulders were placed in the "attention position," an accuracy of 100 per cent on the affected side.

4. One hundred and eight presumably normal controls were studied. Only 4 had positive reactions to tests, and of these, 3 were found on further study to be suffering from the costoclavicular syndrome. Only 1 patient who was symptom free gave a positive reaction, which indicates that the test is over 99 per cent accurate.

5. Some patients were benefited by exercises aimed at strengthening the levator scapulae and trapezius muscles, although the follow-up was not adequate. If exercises fail, scaleniotomy and removal of the cervical rib or a portion of the first thoracic rib is recommended. Excision of the middle third of the clavicle is suggested as another possible method of therapy in intractable cases but it has not been tried.

EXPERIMENTAL STUDIES IN VASCULAR REPAIR

II. Strength of Arteries Repaired by End to End Suture, with Some Notes on Growth of Anastomosis in Young Animals

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CONSIDERABLE knowledge has been accumulated concerning the healing of arteries repaired by suture, the technical features of the operative procedure which favor a successful result and the influence of certain local pathologic processes on the outcome. Little or nothing is known about the strength of the sutured artery or the increase in circumference of the line of anastomosis during the period of body growth. The experiments herein recorded were carried out in an effort to answer the following questions: Does the artery repaired by end to end anastomosis have great or little resistance to disruption when tension is made on the suture line by direct pull? Does the repaired artery have great or little resistance to bursting from intraluminal pressure? Is there a curve of arterial healing similar to those established for the healing of other tissues? Does the line of suture in the anastomosed artery increase in size with increase in size of the artery itself in the growing animal? It was believed that an answer to these questions might make possible more intelligent management of patients for whom vascular repair was necessary.

STRENGTH OF THE ARTERY AS MEASURED BY BURSTING EXPERIMENTS

The experiments were carried out on adult dogs. With the use of sodium pentobarbital and with aseptic precautions, the common carotid arteries were exposed, divided and sutured end to end according to methods previously described.[1]

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This study was aided by a grant from the Office of Naval Research, the United States Navy.

1. Shumacker, H. B. Jr., and Lowenberg, R. I.: Experimental Studies in Vascular Repair: I. Comparison of Reliability of Various Methods of End-to-End Arterial Suture, to be published.

No anticoagulants were used. The dogs varied considerably in size, breed and age. They were all fed the ordinary laboratory diet. Specimens were removed at varying intervals after operation. They were stripped of the very loose external adventitia, moistened with saline solution and immediately subjected to increasing intraluminal pressures until bursting of the line of anastomosis or of the unsutured portion of the artery occurred.

After preliminary studies with mercury manometers, which were found inadequate because of the very high pressures required, and with various methods of producing pressure for the injection, the apparatus depicted in figure 1 was devised. A carbon dioxide tank was connected through a needle valve with a copper tube introduced into the upper portion of the side of a discarded small oxygen tank.

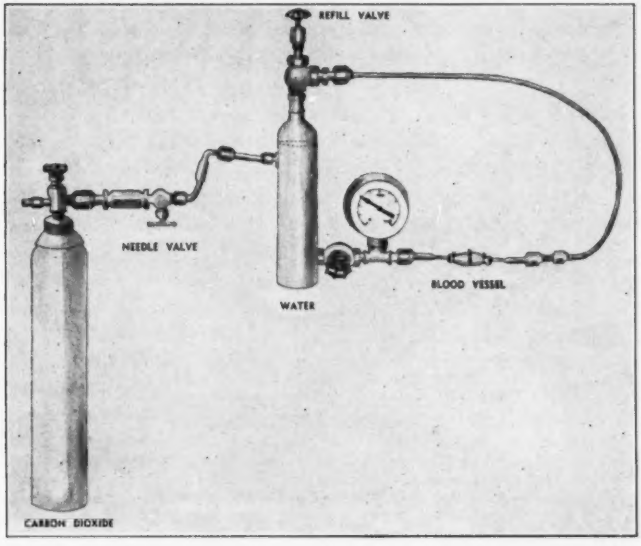

Fig. 1.—Apparatus used in the experiments to determine bursting points.

Another tube emerging from the lower portion of this tank was connected with a pressure gage recording up to 200 pounds and with a small metal cannula. A second cannula was fitted to the end of another tube connected with the top of the tank. The latter tube was used for filling the tank with water. This could be accomplished by opening the top valve on the upper side arm and aspirating water through the tube into the tank. The tank was kept nearly full with water at all times. Except when opened for refilling of the tank, the top valve was kept closed. The freshly removed specimen was secured into the circuit by fixing the two cannulas into the ends of the artery and ligating the vessel about the cannulas with heavy braided silk.

With the needle valve closed, the main valve on the carbon dioxide tank was then opened. The needle valve was turned just sufficiently to permit a slow, steady

increase in pressure. It was not possible to regulate precisely the rate of increase in pressure. However, the procedure was always carried out by the same person, and an effort was made to have a comparable rate of increase of pressure in all experiments; it is believed that little variation occurred. Close watch was kept on the gage and the adjacent vessel. If a leak in the suture line or through the artery wall occurred before bursting, the pressure at which this took place was recorded. The increasing pressure was continued until either the line of anastomosis or the vessel wall broke; the pressure at which this event took place was similarly recorded. The point of bursting was taken as that at which the leak was sufficiently great to cause cessation in rise of pressure as recorded on the gage, or a tendency for the pressure to fall. It will be noted that the water entered the artery at one end and that the pressure continued to rise as the pressure in the tank was increased and as the fluid and air in the long refilling arm became compressed, until equilibrium was reached. In a sense, this arrangement simulated the driving force of the heart and the resistance of the distal vascular bed.

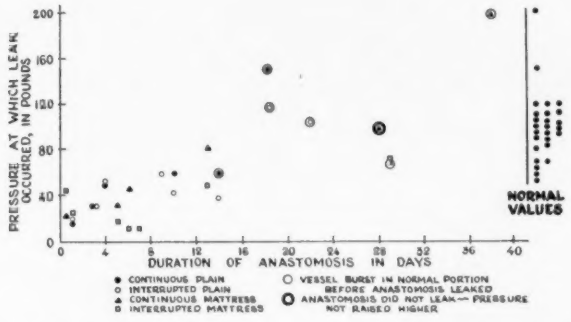

Fig. 2.—Strength of arteries repaired by end to end suture, as indicated by the intraluminal pressure at which a leak at the suture line first occurred. In this chart, as well as in figure 3, the values for the specimen studied thirty-eight days after repair may not be entirely accurate, since some technical difficulty with the apparatus was encountered at that time.

In figure 2, the pressures are recorded at which the anastomosis first began to leak and are compared with values for the normal carotid artery. Twenty-eight observations were made on leaking of the suture line. Twenty-six observations are recorded of the point at which the normal vessel first leaked or at which it burst in those instances in which the initial leak was simultaneous with bursting of the vessel wall. Several facts are evident. In the first place, there was a fairly wide variation. In spite of the variable results, however, it will be seen that the general trend toward increase in resistance to leaking along with an increase in the age of the anastomosis corresponds roughly to the type of curve which has been found representative of the gain in

strength of other sutured tissues. It is evident that the repaired artery withstands, without leaking, pressures far in excess of arterial pressures encountered even in hypertension. In eight hours the pressures at which a leak first occurred were 22 and 46 pounds, or 1,113 and 2,326 mm. of mercury. The lowest pressure at which any of the anastomoses was found to leak was 12 pounds, or more than 600 mm. of mercury. It is seen that the pressures at which a leak occurred increased rapidly with the duration of the anastomosis. Only 2 of the 14 specimens examined within seven days first developed a leak at pressures as high as the lowest normal values, whereas all but 2 of the 14 specimens tested after nine days or longer leaked at pressures at or above the lowest normal values. Furthermore, it will be noted that of the 9 arteries tested fourteen days or more after repair, all save 3 failed to leak at all at pressures at which the normal portion of the vessel wall leaked or burst; 1 of the 3 arteries did not leak at 100 pounds, which was the maximal pressure to which it was subjected. These observations tend to indicate that the sutured artery rapidly regains relatively normal resistance to high intraluminal pressures and that after fourteen days or longer it tends to be more resistant to leaking than is the normal artery.

In figure 3, pressures are recorded at which the line of anastomosis and the normal artery burst. It will be seen that the curve is similar to that recorded in figure 2. There was greater variation in values obtained within the first week after repair. In a comparison of the two charts, it will be seen that there was often a significant difference in the pressures at which any given anastomosis first leaked and then finally burst, whereas the normal artery wall tended to burst at pressures only slightly higher than those at which a leak first occurred, or burst simultaneously with the first leak. Eight hours after repairs the pressures at which the suture line burst were 40 and 60 pounds, or somewhat over 2,000 and 3,000 mm. of mercury, respectively. Twenty-four hours after repair the values ranged from 22 to 95 pounds. As early as five days after repair one suture line failed to burst at a pressure sufficient to burst the unsutured portion of the artery. After two weeks all but 3 of the 9 vessels tested did not burst at pressures sufficient to burst the normal portion of the artery, and 1 of the 3 vessels did not leak at the highest pressure (100 pounds) to which it was subjected. In both figures 2 and 3, values with different methods of repair are indicated. In view of the rather wide variation in results and the small numbers in each group, it is felt that no conclusion can be reached concerning the relative resistance of various types of anastomosis to high intraluminal pressure.

It is apparent that in studies such as these it would be desirable to correlate the thickness of the wall of each individual artery with the pressure at which a leak or burst occurred. Since the pressure is evenly distributed to all portions of the wall of a tubular structure, the resistance to rupture is dependent chiefly on the thickness of the wall and the innate characteristics of the tube. It is, unfortunately, not possible to measure accurately the thickness of the wall of an artery. It varies with spasm or dilatation of the vessel. If the vessel is compressed between two glass slides and the space between is measured to yield twice the thickness of the artery wall, the results differ according to the pressure made on the vessel. If in each case the sutured portion of the artery and a normal intact segment had been tested separately, one could have expressed the result in percentage of normal. This was

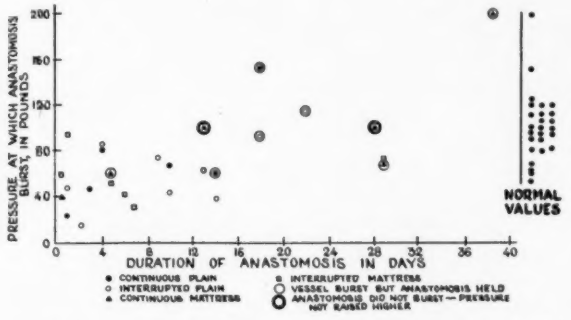

Fig. 3.—Strength of arteries repaired by end to end suture, as indicated by the intraluminal pressure at which the suture line burst.

not done. In each instance, however, we made careful observations to see whether the line of the anastomosis or the normal portion of the artery first give way; as we have pointed out, many of the suture lines failed to leak or burst at pressures which ruptured the artery itself.

It is not surprising that there was considerable variation in the results. The dogs varied in size and age and the size of the carotid arteries differed considerably. Furthermore, it is almost certain that we were never able to strip precisely the same amount of adventitia from all the vessels. That the adventitia lends strength to the vessel is evident. One portion of a control artery with its adventitia intact was found to burst at 62 pounds, for example, while an adjacent portion of the same vessel carefully stripped of the gross external adventitia burst at a pressure of only 24 pounds.

BREAKING FORCE NECESSARY TO PULL APART THE SUTURED ARTERY

Adult dogs were operated on as described in the previous section. All the end to end sutures were carried out with the continuous mattress technic. At varying intervals after operation the specimens were excised. The diameter of the artery was measured, and the loose adventitia was removed. Sufficient length of the artery was excised to permit testing of both the segment containing the suture line and an adjacent normal segment. A number of normal carotid arteries of dogs were similarly prepared for study. The specimen was then measured as carefully as possible. In order to calculate the cross sectional area of the sutured artery, the vessel was gently compressed between two glass slides of known thickness. The thickness of the two slides and the interposed compressed artery was measured with a micrometer accurate to 0.001 inch (2.5 mm.). Simultaneously, the width of the compressed vessel was measured with a ruler of similar accuracy. The artery being compressed between the slides, its cross sectional area was converted for all practical purposes into a rectangle. Presumably, any diminution in thickness by too much compression would result in a corresponding increase in width. By subtracting the thickness of the two slides from the first measurement and multiplying the remainder by the second measurement, the surface area of a cross section of the vessel was obtained. These measurements were made by one observer.

As soon as the measurements were completed, the artery was again moistened with solution of sodium chloride and was divided into two segments, each of which was tested on a Henry L. Scott apparatus designed for determining the tensile strength of suture materials. Each end of the specimen was fixed in the metal jaws of the machine after the ends of the vessel had been carefully wrapped in gauze so as to prevent tearing of this portion of the vessel wall from the pinching force of the clamps. One of the clamps was attached to a gage which recorded force in pounds of pull and could be read in increments of ⅛ pound. An automatic device fixed the indicator at the point at which breaking occurred. The other clamp was attached to a cable on which a pull was exerted by the turning of a large wheel. The increase in pull exerted was at a nearly uniform rate. The sterilized 000000 Deknatel suture used in the vascular suture broke in single strands at a force averaging ¼ pound.

The force necessary to break normal carotid arteries varied from 3.87 to 10 pounds. The force necessary to break the anastomoses varied rather widely (table). It was our hope that consideration of the surface area would yield more information concerning the rate in gain of strength of the sutured artery. However, the same wide variation in the force necessary to pull apart sutured arteries and normal arteries was found. The figures for the normal arteries ranged from 658 to 1,810 pounds per square inch, with an average of 1,224 pounds. When two carotid arteries from the same animal were tested, there was often close correlation of the two in the breaking force and in the "tensile strength" in pounds per square inch; in some, however, the figures for the two arteries were very different. The tensile strength of one, indeed, was nearly twice that of the contralateral artery.

When the breaking force of the suture line was compared with that of an adjacent segment of the same artery and the result expressed in the percentage of normal, a curve was obtained which appears to denote the real trend of the gain in strength of the sutured vessel. In figure 4, these data are plotted in comparison with similar data recently obtained by Fast, Nielsen and Dennis [2] for healing of abdominal wounds. These authors studied the force necessary to pull apart the abdominal wall of rabbits after having made and repaired a rectus incision. The silk sutures were left intact, and the abdominal wall as a whole was tested except for the skin, which was removed. By performing identical studies of the normal abdominal wall on the other side of the midline, they were able to express the results in percentage of normal. It will be seen that our data follow the mean curve of Fast,

Force Necessary to Pull Apart Anastomoses

	Duration of Anastomosis, in Days	Breaking Force, in Pounds	"Tensile Strength," in Pounds per Square Inch
Sutured arteries.....	3	2.125	352
		3.125	727
	6	3.375	485
		1.875	582
	10	3.75	765
	14	5.375	1,340
	20	5.375	1,220
		6.5	1,470
	22	3.875	626
	28	4.0	658
	34	3.5	555
	40	6.375	776
Normal arteries.....	Range	3.875—10	658—1,810
(32 specimens)	Average	6.8	1,224

Nielsen and Dennis surprisingly closely, only the value for the thirty-four day specimen falling far from their curve.

It is not surprising that the absolute values for our normal and sutured arteries varied widely. As applied to metallurgy, tensile strength is the quotient of the force employed and the cross sectional area of the object within the elastic limit of that particular material. In our studies, the determinations have been carried to the breaking point and hence might better be termed studies of disruptive strength than studies of tensile strength. Since, however, a small increment of force reflects an appreciably larger strain on the material once the elastic limit has been reached, only a small difference in force exists between tensile and disruptive strength. Unfortunately, measurement of the cross sectional area of the artery by the method we employed is undoubtedly subject to considerable error, though the method is osten-

2. Fast, J.; Nielsen, C., and Dennis, C.: Rate of Gain in Strength in Sutured Abdominal Wall Wounds, Surg., Gynec. & Obst. **84**:685-688, 1947.

sibly sound. In addition, there are certain variables which cannot be controlled. Precisely the same amount of adventitia cannot be removed from each specimen, and, as we have pointed out before, the adventitial layer imparts a great deal of strength to the vessel. There are undoubtedly variations in the strength of arteries from one animal to another, and from one artery to another in the same animal. In such an experiment as we have performed it is impractical to use litter mates for study, though this might have been advantageous. It appears, however, that comparison of the sutured and normal segments of the same artery and calculation of results in percentages of normal is a sound method for evaluating the strength of the anastomosis.

INCREASE IN SIZE OF ANASTOMOSIS IN GROWING ANIMALS

Both common carotid arteries of 4 small puppies were divided and anastomosed with continuous mattress sutures. As the animals and

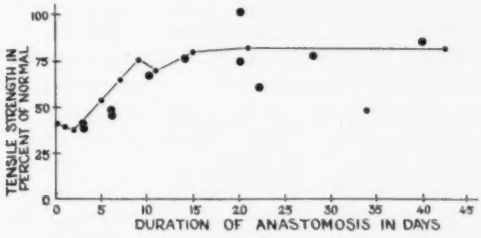

Fig. 4.—Strength of arteries repaired by end to end suture, as measured by the force necessary to pull apart the line of anastomosis. The data are expressed in percentage of normal, the normal values in each instance being determined by pulling apart an adjacent normal portion of the repaired artery. The experimental data are recorded as large solid circles and are compared with the mean curve obtained by Fast, Nielsen and Dennis for gain in strength of the sutured abdominal wall.

their carotid arteries grew in size, the line of suture appeared to increase in size correspondingly. The vessels of 2 dogs were examined approximately one month after suture, and the diameter of the 4 sutured vessels was the same at the line of suture as that of the unsutured portion of the artery. The vessels of 2 dogs were examined six months later. The dogs had gained in weight from 2.9 to 9.8 Kg. and from 5.1 to 14.5 Kg., respectively. The diameters of the carotid arteries had increased between 30 and 45 per cent. The line of anastomosis appeared to be quite as large as the remainder of the vessel. Since these preliminary studies seemed to indicate that the sutured portion of an artery grows with the growth of the vessel itself, no further experiments were conducted.

COMMENT

The studies presented demonstrate that the artery recently repaired by end to end suture breaks with relative ease when tension is placed on the line of suture by direct pull but withstands exceedingly high intraluminal pressure without leaking or bursting. If our relatively small number of observations can be interpreted as demonstrating the gross trend of healing, we may infer that the repaired artery has only about one-third the normal strength to resist disruption by direct pull during the first few days but has about three-quarters the normal strength by the end of the second week. Our studies demonstrate that the repaired artery, on the other hand, will withstand, without leaking, pressures many times as high as systolic blood pressure even within a few hours after repair, and that it is likely to be more resistant to leaking with high pressures than the unsutured portion of the artery after two weeks have passed. These experiments indicate clearly that one need have little fear of disruption of the sutured artery from the force of the blood pressure. If the anastomosis is left dry and has been accomplished without tension, there is little or no hazard of subsequent disruption and hemorrhage. If the ends of the artery can be approximated only by relaxation of tension by proper posturing of the part, as is sometimes necessary in the surgery of aneurysms and fistulas of the axillary, brachial, popliteal and other peripheral vessels, one must maintain the extremity in the optimal position for some time. We do not feel that our studies yield conclusive evidence concerning the necessary length of time for avoidance of tension on the suture line after repair, but they suggest that at least a two week period, and perhaps a longer time, is essential. In certain vascular operations vessels which appear capable of being brought together only under tension can be successfully approximated, as is not infrequently the case in the subclavian-pulmonary artery operation of Blalock.[3] In none of these cases has disruption occurred. It is entirely likely that when vessels can be brought together with 00000 or 000000 silk sutures one can assume that they are held without undue tension.

The ultimate functional success of vascular anastomoses in the young depends on the growth in size of the suture line as the artery increases in circumference. Otherwise, the result would be compromised by development of a functional stricture. Our preliminary observations suggest that the circumference of the line of anastomosis and that of the unsutured wall of the artery increase comparably.

Our studies throw some light on the rate of healing of the sutured artery and indicate that the trend of gain in strength is comparable to

3. Blalock, A.: Physiology and Surgical Treatment of Congenital Cardio-Vascular Defects, Bull. New York Acad. Med. **22**:57-80, 1946.

that observed in other tissues by Harvey and his associates and by others.[4] We should like to emphasize, however, that our studies are not presented as representing statistically accurate curves of gain in strength. In most such experiments absorbable suture material has been used so that the tests could be performed on tissues free of sutures; in our studies the tests were performed on anastomoses with the original silk sutures intact. We have pointed out the role of the adventitia in the strength of the sutured artery and the improbability that the adventitia can be stripped to a precisely comparable degree in each specimen. We have also discussed certain other possible variables, such as weight, size, age and breed of the animal. In addition, though we have carried out sufficient studies to indicate the trend, we have not performed the numerous experiments which would be necessary to establish a statistically significant mean curve of increase in strength. It is of interest that the trend demonstrated is quite similar to the curves established for the healing of other tissues. The data obtained with our determinations of the breaking force followed remarkably closely the curve for gain in strength of the abdominal wall with intact silk sutures presented by Fast, Nielsen and Dennis. Our studies would indicate that any future experiments designed to establish more precisely the rate of increase in strength of the sutured vessel may best be expressed in percentage of normal of the vessel which itself was used for the repair.

CONCLUSIONS

1. The artery anastomosed by end to end repair appears to gain in strength in a fashion similar to that of other sutured tissues.

2. The force necessary to break the recently sutured artery by direct pull is not great, but the sutured artery withstands, without leaking, intraluminal pressures far in excess of systolic blood pressure.

3. Preliminary studies indicate that the circumference of the artery at the line of anastomosis increases in the growing animal comparably to the increase in circumference of the unsutured portion of the artery.

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RETROCAVAL URETER

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THE VASCULAR anomaly which results in a venous trunk lying anterior to the ureter so that the latter structure must completely encircle it en route to the bladder has been variously described as a postcaval ureter, a precaval ureter and a circumcaval ureter. We are unable to offer a more accurately descriptive term, but it must be realized that although these terms would suggest a ureteral anomaly it is actually a vascular abnormality. That this vascular variation is premiant is attested by the fact that the case reported herein is the thirty-seventh recorded instance, and only twice previously has the diagnosis been made preoperatively. This condition, by virtue of its infrequence and the associated potential seriousness of the resultant lesion along with the complexity of its surgical correction, demands more frequent preoperative diagnosis. The treatment will be discussed in the light of the present exiguous literature and the reported cases analytically tabulated.

The embryologic considerations have been discussed in varying detail in numerous reports and will be omitted in this paper. Suffice it to say that this rarest of congenital anomalies is due to vascular variation by the persistence of one of the embryonic veins during the formation of the vena cava and that the obstructive uropathy is an incidental occurrence. Ureteral obstruction with hydroureter or pyelectasis or both was recorded in 24 of the 36 cases previously reported. In 1 case the status of the urinary tract was not reported. The cause of the obstruction in our opinion is dependent more on the ureter being wedged in the crotch formed by the vena cava and the vertebral vein than on pressure between the vena cava and the posterior abdominal wall or between the vena cava and the aorta.

SYMPTOMATOLOGY

The subjective findings vary from those of ureteral colic to those of intractable pyelonephritis and hematuria. Some of the patients are asymptomatic and the condition is first observed as an incidental finding at necropsy.

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DIAGNOSIS

A preoperative diagnosis has been made on only two previous occasions (Harrill; Greene and Kearns). In Harrill's patient the symptoms of ureteral obstruction were evident, and the diagnosis was made by means of stereoscopic pyelograms. In the case reported by Greene and Kearns a calculus had been passed previously, and shortly before the diagnosis of circumcaval ureter was made the patient experienced severe ureteral colic associated with hematuria. The diagnosis was established since the pyelograms revealed distention of the upper part of the ureter, which ended abruptly when the ureter passed over the body of the third lumbar vertebra in a superior and medial direction. In our case the diagnosis was made on essentially the same criteria as those described by Greene and Kearns.

The most suggestive diagnostic criteria for circumcaval ureter are as follows.

A. In the lateral roentgenograms the ureter, instead of maintaining a position distinctly anterior to the vertebral column in the region of the third or fourth lumbar vertebral bodies, lies in close apposition (Randall and Campbell).

B. The stereoscopic pyeloureterograms demonstrate the ureteral curvature to be such as "to include a structure having the diameter and position of the vena cava" (Harrill).

C. The ureter is displaced toward and generally overlies the midline, usually in the region of the third and fourth lumbar vertebra.

D. The ureter presents in its upper portion a falciform curve, and if there is present obstruction the ureterectasis ends abruptly at the medial portion of the curve as it courses downward and overlies the third and fourth lumbar vertebrae.

E. The abnormality is a lesion on the right side and has been known to occur bilaterally only once and that in an acardiac monster with a bilateral vena cava (Gladstone).

TREATMENT

In 6 of the 36 patients reported on a primary nephrectomy was employed. These patients constitute part of the group of 15 surgically treated patients (Randall and Campbell; Derbes and LaNasa; Shih; Gruenwald and Surks; Wilson and Herzlich). In one instance a secondary nephrectomy was necessary since after the plastic repair of the ureteral abnormality calculi and infection intervened (Nourse and Moody).

In the case reported by Young a calculus was removed from the upper part of the ureter and no further surgical procedure undertaken

since it was felt that the anomaly was of no obstructive significance. The author's postoperative observations were reported to have substantiated this decision.

Various types of plastic procedures on the ureter were done in 7 instances (Kimbrough; Uebelhör; May; Harrill; Greene and Kearns; Lowsley; Nourse and Moody). The plastic operation most commonly employed was section and reanastomosis of the ureter after its removal from around the vena cava. To Kimbrough goes the distinction of first observing a postcaval ureter at operation and successfully performing ureteral section and reanastomosis. Harrill was the first to diagnose this condition preoperatively. He divided the renal pelvis, and after the ureter was freed from its caval position the pelvis was reanastomosed. Lowsley, on the other hand, divided the ureter at its vesical extremity and after removing it from the vena cava reimplanted it into the bladder. Because of a ureteral stricture in its immediate superovesical portion a second operation was necessary. This was followed by the development of an abscess which devitalized the ureter, and a cutaneous ureterostomy was the final solution.

It seems to us that in instances in which the renal destruction has not progressed to an irreparable stage a plastic operation or a combination of such procedures is the therapeutic solution. Furthermore, the actual excision of the ureteral stricture would seem to offer permanent success.

In the following table the various cases recorded are tabulated. It will be noted that there are 27 males in this series. As several authors have pointed out, the preponderance of males is probably due to the fact that most of the persons were seen as cadavers and in this group males predominate. In the operative cases it will be seen that again the males predominate; however, the series is too small to be of statistical significance. In 24 instances of retrocaval ureter there was an associated obstructive uropathy.

There have been reported a total of 36 persons with retrocaval ureter during the past fifty-four years. All patients were seen on the dissecting table until 1935, when Kimbrough observed the first patient at operation. Harrill, in 1940, was the first to diagnose this abnormality preoperatively.

REPORT OF A CASE

A farmer of 44 years consulted us on the advice of his family physician because of a recent attack of ureteral colic on the right side associated with hematuria. His subjective symptoms were relieved after two injections of morphine.

On physical examination nothing of note was discernible. The urinalysis showed moderate pyuria with microscopic hematuria. Studies of the blood

Chronologic Tabulation of Cases Reported

Author	Year	Sex	Age	Obstructive Uropathy	Time of Diagnosis	Comment
Hochstetter	1893	M	Weeks	No	Necropsy	
Gladstone	1906	M	Term	No	Necropsy	Acardiac fetus
Kolisko	1909	M	55 yr.	Yes	Necropsy	
Gladstone	1909	M	84 yr.	Yes	Necropsy	
Jacobson	1927	M	72 yr.	Yes	Necropsy	
Jacobson	1927	M	1 yr.	No	Necropsy	Renal agenesis, left
Wicke	1927	M	58 yr.	No	Necropsy	
Kengyel	1928	F	57 yr.	Yes	Necropsy	
Gierke	1928	M	16 yr.	Yes	Necropsy	
Skamnakis	1931	M	50 yr.	Yes	Necropsy	
Kimbrough	1935	M	20 yr.	Yes	Operation	First patient seen clinically; lesion diagnosed at second operation and successfully repaired by section and reanastomosis
Rotter	1935	M	49 yr.	Yes	Operation	Double postrenal vena cava, right
Rotter	1935	..	.....	No	Necropsy	Bilateral postrenal vena cava
Randall and Campbell	1935	F	25 yr.	Yes	Operation	Nephrectomy
Randall and Campbell	1935	F	55 yr.	Yes	Operation	Nephrectomy
Derbes and Dial	1936	?	Adult	Yes	Necropsy	
Derbes and Dial	1936	?	Adult	Yes	Necropsy	
Uebelhör	1936	F	36 yr.	Yes	Operation	Ureteral section and reanastomosis; nephrostomy and nephropexy; recovery
Derbes and LaNasa	1937	F	42 yr.	Yes	Operation	Nephrectomy
Wren	1937	M	Adult	No	Necropsy	
Shih	1937	M	44 yr.	Yes	Operation	Nephrectomy
Adachi	1937	M	42 yr.	?	Necropsy	Bilateral postrenal vena cava
Adachi	1937	F	40 yr.	No	Necropsy	Bilateral postrenal vena cava
May	1938	M	17 yr.	Yes	Operation	Ureteral section and reanastomosis; pyelotomy; nephrostomy; nephropexy
Palazzi, Rached, Sanchez and Rincon	1939	M	Adult	No	Necropsy	
Antopol and Yelin	1939	F	72 yr.	Yes	Necropsy	
Pick and Anson	1940	M	44 yr.	No	Necropsy	
Harbach	1940	M	20 yr.	Yes	Operation	Nephrectomy
Harrill	1940	M	46 yr.	Yes	Preoperative	First instance of preoperative diagnosis; ureter passed around double vena cava; section above the ureteropelvic junction with reanastomosis
DeCarlo	1941	M	60 yr.	No	Necropsy	
Gruenwald and Surks	1943	M	Adult	No	Necropsy	
Wilson and Herzlich	1944	M	21 yr.	Yes	Operation	Nephrectomy
Nourse and Moody	1946	M	21 yr.	Yes	Operation	Unsuccessful ureteral anastomosis due to calculus; nephrectomy
Greene and Kearns	1946	M	29 yr.	Yes	Preoperative	Ureteral section and reanastomosis
Lowsley	1946	M	44 yr.	Yes	Operation	Ureteral section at the bladder with reimplantation, nephrostomy; subsequent abscess at the site of vesical implantation requiring cutaneous ureterostomy (left kidney nonfunctional)
Young	1947	F	24 yr.	Yes	Operation	Cause of obstructive uropathy thought to be ureteral calculus rather than the postcaval ureter and for this reason the calculus was removed and no plastic procedure done to change the course of the ureter; disappearance of ureteral dilatation observed 8 months postoperatively

revealed no anemia and a normal cytologic picture. Chemical examination of the blood and immunologic studies revealed nothing abnormal.

The cystoscopic examination revealed a slightly edematous right ureteral orifice but no other signs of vesical abnormality. On the introduction of ureteral catheters into both renal pelves the left kidney was found to be normal functionally and morphologically. The right kidney was virtually functionless as studied on the basis of excretion of dye. The ureteropyelogram demonstrated a markedly hydronephrotic pelvis and calyxes with the upper region of the ureter dilated. This region prescribed a typical falciform curve, with the terminal portion of the

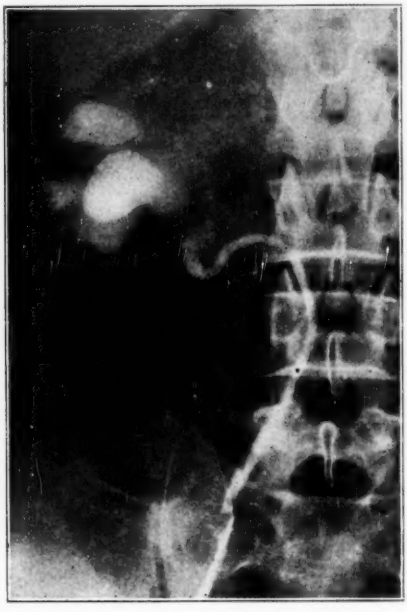

Fig. 1.—Ureteropyelogram showing falciform curve in ureter which in its lower portion overlies the body of the third lumbar vertebral body.

dilated ureter overlying the third lumbar vertebral body and at this point crossing the midline of the body. It was on the basis of this last criterion that the diagnosis of retrocaval ureter was made which was confirmed at operation.

At operation the right kidney was found to be greatly enlarged. The pelvis was huge, and the upper portion of the ureter took a normal downward course and then suddenly turned and passed under the vena cava. When a portion of the vena cava was isolated below the point where the ureter passed under this structure, the ureter was again visualized as it emerged from behind the vessel, and after encircling the vessel it proceeded in a normal course toward the bladder. At the pelvic brim the ureter had assumed its normal relationship with the iliac

vessels. The ureter was severed near the bladder after ligation and dissected free. It was found difficult to extract the ureter from under the vena cava, and for this purpose it was necessary to mobilize the vena cava partially. The hydronephrotic portion of the ureter suddenly ceased at the point behind the vena cava where the ureter was wedged in a crotch formed by a vertebral vein and the vena cava. It would seem that this relationship was the cause of the hydronephrosis rather than the abnormal association of the ureter and the vena cava. After the ureter was entirely free and removed from behind the vena cava the renal pedicle was ligated and the kidney and ureter removed.

The patient's postoperative course was uneventful, and he has enjoyed an active, healthy existence during the past eighteen months.

Fig. 2.—Operative specimen showing pyelectasis and the course of the ureter in its circumvascular path around the vena cava, which is represented by the test tube.

SUMMARY

An additional case of retrocaval ureter is added to the existing literature, which brings the total number of reported cases to 37. The patient was subjected to nephrectomy and ureterectomy because of an inadequately functioning kidney.

The literature is reviewed, and the previously reported cases have been tabulated. A complete bibliography is appended.

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ACUTE MESENTERIC LYMPHADENITIS

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ACUTE mesenteric lymphadenitis is a symptom complex characterized by abdominal pain and tenderness. For the patient suspected of having this condition, the presence of acute appendicitis cannot be excluded either by the history, the physical examination or the laboratory findings. Because of this difficulty in differentiation, with rare exceptions operation is urgently indicated when either diagnosis is made.

During the five years between July 1, 1941, and Aug. 1, 1946, there were admitted to Duke Hospital 1,604 patients with the symptoms and signs of an acute condition in the abdomen which led to treatment by appendectomy. Of these, 931 had acute appendicitis. The remaining 673 patients had grossly normal appendixes; in this group, no cause for the abdominal pain was found in 185 patients, while 220 patients had one of a large number of diseases, the most common being hemorrhage from a ruptured graafian follicle, pelvic inflammatory disease and gastroenteritis. In 268 of the 673 patients with grossly normal appendixes, enlargement of mesenteric lymph nodes was encountered, and for these the diagnosis was nonspecific mesenteric lymphadenitis. Thus 1 patient in every 6 admitted because of an acute condition within the abdomen and treated by means of appendectomy had mesenteric lymphadenitis.

In spite of the frequent occurrence of acute mesenteric lymphadenitis, little definite information is available regarding the etiology, and considerable difference of opinion exists as to accuracy of differential diagnosis and proper treatment. Wilensky,[1] who has contributed several important summaries on the etiology as well as other aspects of mesenteric lymphadenitis, expressed the belief that it is a secondary

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1. Wilensky, A. O.: (*a*) General Abdominal Lymphadenopathy with Special Reference to Nonspecific Mesenteric Lymphadenitis, Arch. Surg. **42**:71-125 (Jan.) 1941; (*b*) Chronic Intra-Abdominal Lymphadenopathy with Special Reference to Chronic Nonspecific Mesenteric Adenitis, Surgery **9**:787-820 (May) 1941; (*c*) Acute and Chronic Intra-Abdominal Lymphadenopathy, Surg., Gynec. & Obst. **72**:1060-1069 (June) 1941.

manifestation of another process in the body, usually infectious. Ireland [2] has also summarized the suggested possible causes, which range from a foreign body to a virus. Many [3] believe that the appendix usually serves as the portal of entry for the offending agent. Wilensky [1] and Klein,[4] however, were of the opinion that only a congenital anomaly of the lymphatic drainage of the appendix may incriminate this structure as the site of the initial lesion.

Gage [5] has reported positive cultures of 93 per cent of 65 nodes removed, but others [6] have found the nodes usually sterile. Oxyuris vermicularis in the appendix was found by Ingegno [7] in 1 case, by Ireland [2] in 1, by Marshall [6d] in 6 and by Heusser [6a] in several cases. No cultures of a virus have been reported, although a virus has been suggested as the causative factor. Definite proof of a single etiologic agent is lacking.

Since the comprehensive papers by Wilensky in 1941 and the review by Postlethwait, Self and Batchelor [8] in 1942, several publications have appeared which are of interest particularly from the

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standpoint of differential diagnosis and indications for operation. Bothe and Pote [9] reviewed 154 cases and stated that abdominal exploration should be performed in all instances:

> . . . first, lest an acute appendix which should be removed be overlooked; second, because laparotomy seems to be beneficial to the condition and may reveal any obstructive adhesions which should be corrected; third, because the type of after-treatment is influenced by the presence or absence of lymphadenitis; and fourth, because any possible portal of entry of infection should be removed.

Braithwaite [10] discussed the mechanism of production of gastric symptoms, particularly pylorospasm, by ileocecal disease, giving the etiologic factors as chronic appendicitis, nonspecific ileocecal adenitis and tuberculous ileocecal adenitis. He felt that ileocecal adenitis could be diagnosed from the presence of spasm of the lower portion of the ileum and the ileocecal valve, as demonstrated by roentgenologic studies. Fifteen cases of chronic ileocecal adenitis were reported. Tilley [11] reviewed his 69 cases and concluded that "operation with removal of the appendix is indicated when acute appendicitis cannot be ruled out; with a probable diagnosis of mesenteric lymphadenitis, treatment should be conservative."

King [12] reported on 84 patients and stated: "It is as yet impossible to diagnose the lesion definitely without laparotomy." Nevertheless, in 35 of his 84 cases no operation was performed. He reported on a patient hospitalized three days and then discharged with a diagnosis of mesenteric lymphadenitis. The patient returned one week later with a perforated appendix and abscess. Aird [13] observed 37 cases of mesenteric lymphadenitis in one year, but he stated that this figure was only an approximation as "a considerable number of children in whom a diagnosis of nonspecific adenitis has been made in the outpatient department have not been admitted but have been confidently allowed to go home." Coleman [14] stated, in a more recent review of his cases, that immediate appendectomy was routinely advised because "we have seen too many instances in which our preoperative diagnosis was

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9. Bothe, F. A., and Pote, H. H.: Mesenteric Adenitis Associated with Appendicitis, Internat. Clin. **4**:77-88 (Dec.) 1941.

10. Braithwaite, L. R.: Ileo-Gastric Syndrome, Brit. J. Surg. **30**:15-22 (July) 1942.

11. Tilley, J. H.: Acute Nonspecific Mesenteric Lymphadenitis, Am. J. Surg. **57**:472-476 (Sept.) 1942.

12. King, W. E.: Acute Nonspecific Mesenteric Adenitis, Am. J. Surg. **64**:92-94 (April) 1944.

13. Aird, I.: Acute Nonspecific Mesenteric Lymphadenitis, Brit. M. J. **2**:680-682 (Nov. 17) 1945.

14. Coleman, E. P.: Mesenteric Lymphadenitis, Am. J. Surg. **72**:879-882 (Dec.) 1946.

mesenteric lymphadenitis but upon opening the abdomen a distended, acutely inflamed appendix was found."

It is evident from these reports that considerable difference of opinion exists with regard to the accuracy of differential diagnosis and whether laparotomy should be done. In these recent publications Bothe and Pote, Braithwaite and Coleman were of the opinion that operation is definitely indicated, whereas Tilley, King and Aird were willing to defer operation, Aird "confidently" allowing the patient to go home.

In an attempt to settle this difference in opinion, the records of the 268 cases of acute mesenteric lymphadenitis observed at the Duke Hospital have been reviewed and compared with the records of 100 unselected cases of simple acute suppurative appendicitis treated during the same period. In addition, follow-up studies by letter or clinic visit were carried out in the group with mesenteric lymphadenitis. The data form the basis of this communication.

INCIDENCE

The comparative incidence of appendicitis and nonspecific mesenteric lymphadenitis has been indicated in the introduction. There were 99 males and 169 females with mesenteric lymphadenitis. Two

TABLE 1.—*Age Incidence*

Age, Yr.....	0 to 5	6 to 10	11 to 15	16 to 20	21 to 25	26 to 30	31 to 40	41 to 50	Over 50
Appendicitis, %.....	1.0	2.0	19.0	31.0	20.0	11.0	8.0	6.0	2.0
Mesenteric adenitis, %	2.3	12.8	30.4	37.2	11.6	3.8	1.5	0.4	0

hundred and fifty-five of the patients were white, 11 were Negro and 2 were Indian. Analysis by seasons was without significance Occurrence by age was charted in table 1, which showed a comparative increase in mesenteric lymphadenitis in the younger age groups.

HISTORY

Only 7 per cent of patients with appendicitis had prior similar attacks whereas 47.4 per cent of patients with mesenteric lymphadenitis had one or more attacks of pain before the episode which caused hospitalization. Duration of symptoms at the time of hospitalization was about the same, as noted in table 2, except that the percentage of patients with symptoms for more than seventy-two hours was greater in the group with mesenteric lymphadenitis.

Abdominal pain was the first and predominant symptom in 96 per cent of patients with appendicitis and in 90 per cent of patients with mesenteric lymphadenitis. The pain began in the right lower quadrant in 39.5 per cent with mesenteric lymphadenitis and in 19 per cent

with appendicitis. In the cases of mesenteric lymphadenitis the pain at onset was periumbilical in 31.9 per cent, compared with 14 per cent in the cases of appendicitis. Epigastric pain was the first noted in 22 per cent of patients with appendicitis and 14.2 per cent with mesenteric lymphadenitis. Generalized abdominal pain occurred first in 23 per cent and pain in both lower quadrants in 14 per cent of the patients with appendicitis, whereas these were rarely the site of onset of pain in mesenteric lymphadenitis. When the pain did not begin in the right lower quadrant, it later localized there in 88 per cent of the patients with appendicitis and 66 per cent of those with mesenteric lymphadenitis.

The character of pain in both groups varied so markedly as to prohibit detailed analysis. It was noted, however, that in cases of appendicitis the pain usually persisted, frequently becoming gradually more severe, whereas with mesenteric lymphadenitis the pain was intermittent and usually colicky when present, with periods of complete freedom from it. The latter type was noted in 28.7 per cent of

TABLE 2.—*Duration of Symptoms*

Duration, Hr	6	6 to 12	12 to 24	24 to 48	48 to 72	Over 72
Appendicitis, %	5.0	16.0	28.0	38.0	12.0	1.0
Mesenteric adenitis, %	6.5	15.8	27.1	22.3	12.1	16.2

the patients with mesenteric lymphadenitis and in only 4 per cent of those with appendicitis.

Nausea and vomiting were slightly more frequent in cases of appendicitis. Diarrhea or constipation occurred in almost exactly the same percentage of patients in each gorup; 11 per cent had diarrhea, and 6 per cent had constipation. Of the patients with mesenteric lymphadenitis, 54.5 per cent gave a history of a recent or persistent infection of the upper respiratory tract or showed signs of such infection on examination.

EXAMINATION

In general, the routine physical examination revealed nothing remarkable, and the findings of principal interest pertained to the abdomen. Tenderness in the right lower quadrant was present in 99 per cent of the patients with appendicitis and in 89.6 per cent with mesenteric lymphadenitis. With appendicitis, tenderness was also present in the left lower quadrant in 30 per cent, the right upper quadrant in 2 per cent and the epigastrium in 1 per cent and was generalized in 1 per cent. Conversely, in patients with mesenteric lymphadenitis there was tenderness in the left lower quadrant alone or in addition in 15.2 per cent, the right upper quadrant in 3.1 per cent and

the epigastrium in 2.2 per cent. In this group it was generalized in 10.4 per cent. The tenderness was more frequently and definitely localized in the right lower quadrant in cases of appendicitis. Although not obvious from the records, the tenderness in mesenteric lymphadenitis, when carefully outlined, was frequently found to extend along the root of the mesentery of the small bowel, i. e., from the right lower quadrant obliquely upward and to the left across the umbilicus. A comparison of signs of peritoneal irritation showed a decided difference. Local rebound tenderness was present in 76 per cent with appendicitis and 35.8 per cent with mesenteric lymphadenitis, referred rebound tenderness was found in 62 per cent with appendicitis and 27.1 per cent with mesenteric lymphadenitis and muscle spasm occurred in 60 per cent with appendicitis and 35.4 per cent with mesenteric lymphadenitis. Tenderness by rectal examination was almost exactly the same (69 and 68.7 per cent).

TABLE 3.—*Temperature on the Patient's Admission to the Hospital*

Temperature, Degrees, F.....	96.8 to 99.5	99.6 to 100.4	100.5 to 101.3	101.4 to 102.2	102.3 to 103.1	Over 103.1
Appendicitis, %.....	48	28	17	4	3	0
Mesenteric adenitis, %	67	15	12	3	1	2

TABLE 4.—*White Blood Cell Counts*

Count.....	4,000-10,000	10,100-12,500	12,600-15,000	15,100-20,000	20,100-25,000	25,100-30,000
Appendicitis, %.....	22	19	21	27	8	3
Mesenteric adenitis, %	49	25	17	7	2	0

The rectal temperature at the time of the patients' admission to the hospital was generally higher in those with appendicitis (table 3). A similar and more pronounced trend was noted in the white blood cell counts (table 4).

PREOPERATIVE DIAGNOSIS

Of the 268 patients, 80 (30 per cent) were given a preoperative diagnosis of mesenteric lymphadenitis. For 73 of the 268 patients mesenteric lymphadenitis was listed in the differential diagnosis but not thought to be most likely, and for the remaining 115 patients mesenteric lymphadenitis was not mentioned. The most frequent preoperative diagnosis was appendicitis.

OPERATIVE FINDINGS

In all the patients with mesenteric lymphadenitis in this series, the appendix was grossly normal at operation. The lymphadenitis was described as slight in 48, moderate in 169 and marked in 51. Consider-

able variation in interpretation of the degree of lymphadenitis was apparent. In the operative notes, associated conditions described were as follows: salpingitis, 2 cases; ileitis, 4 cases; acute Meckel's diverticulitis, 1 case and ureteral stone, 1 case. In all cases the appendix was removed.

PATHOLOGIC PROCESS

No lymph nodes were removed for histologic examination. In the case mentioned previously the impression of acute Meckel's diverticulitis was confirmed. The appendixes were normal pathologically, with the following exceptions: Acute appendicitis was present in 15 cases, subacute appendicitis in 6, chronic appendicitis in 6, fecalith in appendix in 7, obliterated lumen of appendix in 10, pinworms in appendix in 19, lymphoplasia of appendix in 5 and periappendicitis in 3.

POSTOPERATIVE COURSE

Fifty-one patients were febrile after operation. Fifteen had a temperature as high as 39 C. (102.2 F.) which was present for more than one day, and 9 had a sustained temperature over 39 C. The cause was an infection of the upper respiratory tract in 7, pneumonia in 2, bronchitis in 2 and pyelitis in 1. No cause other than the abdominal condition was demonstrable in the others. Four patients had severe nausea and vomiting postoperatively, and diarrhea developed in 1. There was infection of the wound in 1 case and parotitis in another, and in 1 case measles developed. One patient had transitory hematuria postoperatively, which could not be explained.

Follow-up Data.—The present status of 154 of the 268 patients was determined. One had been killed in an accident, and 1 died from an unknown cause. Two patients died of intestinal obstruction, 1 at this hospital and 1 elsewhere. Five other patients were readmitted because of intestinal obstruction, which occurred on two separate occasions in 3 of these.

One hundred and eighteen patients had remained perfectly well after operation, whereas 27, or 17.5 per cent, of the group followed had a recurrence of their pain. The recurrent pain was like that which was present prior to operation. Instances of incisional sensitiveness or menstrual disorder were eliminated as carefully as possible. The number of attacks averaged two or three. These persisted for an hour to several days, but most lasted twelve to eighteen hours. The patients usually felt that their subsequent attacks were less severe, but the majority had residual tenderness for several days. No definite etiologic or precipitating factors could be ascertained by questioning.

COMMENT

The etiology of acute nonspecific mesenteric lymphadenitis remains doubtful, but it is felt that the enlarged lymph nodes probably represent reaction to injurious agents, either bacteria, viruses or their toxins, which originate in the appendix or ileum. The parasites which are occasionally found may provide a point of entry for these agents by mucosal injury.

Patients who had pathologic signs of inflammation in the appendix possibly should not be described as having mesenteric lymphadenitis, as the symptoms and signs were undoubtedly due to the appendical changes in many cases. The inclusion was deliberately made, however, as it is thought that definite pathologic changes would be found much more frequently if opportunity were available for more thorough abdominal exploration and such studies as histologic examination of the ileal wall.

Mesenteric lymphadenitis is an operative diagnosis and can be strongly suspected preoperatively, but a preoperative diagnosis of mesenteric lymphadenitis should necessitate operation as readily as a preoperative diagnosis of acute appendicitis. Nearly half of the reported group of patients with mesenteric lymphadenitis were under 15 years of age, and diagnosis of appendicitis is notoriously treacherous in children because of atypical symptomatology. Actually, atypical appendicitis is common in all age groups, as shown in the summary of 500 cases from this hospital by Gardner and Sapp.[15] Therefore, as acute appendicitis may frequently present atypical manifestations and as mesenteric lymphadenitis may mimic appendicitis in any of its forms, operation is essential to avoid overlooking an acutely inflamed appendix which should be removed.

In an analysis of a large series of cases, statistical differences in the occurrence of symptoms and signs will be noted, yet no single examination or group of findings is adequate to differentiate accurately between acute mesenteric lymphadenitis and acute appendicitis in the individual patient. The morbidity and mortality of simple appendectomy are now so low that the removal of ten or more normal appendixes, with the finding of mesenteric lymphadenitis, is more justifiable than permitting one appendix to perforate, with the resultant complications. In the rare instance in which intercurrent disease or other factors contraindicate operation, conservative treatment of suspected mesenteric lymphadenitis may be necessary. Infrequently the symptoms and signs may suggest mesenteric lymphadenitis and be so mild that the patient is held under careful observation.

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15. Gardner, C. E., Jr., and Sapp, C. J.: Atypical Features in Manifestations of Acutely Inflamed, Nonruptured Appendix, Am. J. Surg. **57**:477-482 (Sept.) 1942.

SUMMARY

Nonspecific mesenteric lymphadenitis is a symptom complex characterized by abdominal pain and tenderness. Many of the patients have a history of prior attacks of pain, and about half have an infection of the upper respiratory tract. The pain usually begins in the right lower quadrant, epigastrium or periumbilical region, and when it does not begin in the right lower quadrant it localizes there in 66 per cent of the patients. It frequently comes in paroxysms, with intervals of complete relief. Tenderness is usually present in the right lower quadrant, but signs of peritoneal irritation occur in only about one third of the cases. The temperature and the white blood cell count may or may not be increased. Of 154 patients followed in this series, 17.5 per cent had recurrence of the same pain. Operation, with removal of the appendix, is strongly advised, as an accurate differential diagnosis between mesenteric lymphadenitis and acute appendicitis cannot be made.

SEVERE INTERFERENCE WITH BILE FLOW IN PRIMARY HEPATITIS

Its Significance in the Differential Diagnosis of Jaundice

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PRONOUNCED interference with the bile flow is, as a rule, characteristic of extrahepatic biliary obstruction, usually of mechanical character, caused by stones, strictures and tumors. Hence surgical intervention is usually considered in cases of such nature. Only rarely is an intrahepatic mechanical obstruction of the larger bile ducts encountered. In contrast to earlier belief, however, interference with bile flow is met not uncommonly in cases of primary hepatitis in the acute or chronic stage. This interference may present complete biliary obstruction characterized by absence of bile from the duodenum and consequent lack of urobilinogen in the urine. In cases of primary hepatitis the phenomenon has been called intrahepatic biliary obstruction, and it has been the subject of several descriptive analyses.[1] Various hypotheses as to the pathogenesis of this phenomenon have been presented.[2] Recently, Watson and Hoffbauer[3] described cases of temporary exclusion of bile from the duodenum in instances of infectious hepatitis in which the damage to the hepatic cells was either subsiding or absent. They called this condition cholangiolitic hepatitis. They assumed damage of the cholangioles, not demonstrable morphologically, which

Aided by a grant from the Jerome D. Solomon Memorial Research Foundation.

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1. (*a*) Lichtman, S. S: Diseases of the Liver, Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942. (*b*) Steigmann, F., and Popper, H.: Intrahepatic Obstructive Jaundice, Gastroenterology **1**:645 (July) 1943.

2. (*a*) Eppinger, H.: Die Leberkrankheiten, Vienna, Julius Springer, 1937. (*b*) Popper, H.: Serose Hepatitis, Wien. klin. Wchnschr. **49**:207 (Feb. 14) 1936.

3. Watson, C. J., and Hoffbauer, F. W.: The Problem of Prolonged Hepatitis with Particular Reference to the Cholangiolitic Type and the Development of Cholangiolitic Cirrhosis of the Liver, Ann. Int. Med. **25**:195 (Aug.) 1946.

may become chronic and which was considered responsible for the backflow of bile into the blood. In subsequent studies [4] they considered this cholangiolar dysfunction the main basis of hepatic jaundice.

In addition to the relatively small number of cases in which prolonged complete biliary obstruction is evidenced by the absence of urobilinogen from the urine, there is a larger group in which some function tests of interference with bile flow reveal pathologic conditions. Some interference with the bile flow is found in every case of regurgitation jaundice, i. e., medical or surgical. This is indicated by the increase of the direct serum bilirubin. However, severe interference with the bile flow as usually noted in cases of extrahepatic biliary obstruction is indicated by increase of the serum alkaline phosphatase and the total serum cholesterol in addition to absence of urobilinogen from the urine and stool. This definition may appear arbitrary, but it permits a workable diagnostic criterion. In general, then, in the presence of jaundice, increase of the serum alkaline phosphatase in the absence of pathologic bone changes, increase of the total serum cholesterol level, reduced urinary urobilinogen and decreased fecal urobilinogen must be considered as evidence of severe interference with bile flow. These findings may be temporary or prolonged. Such cases represent a diagnostic problem because of the difficulty in differentiating them from surgical conditions in which damage to hepatic cells is found in addition to signs of severe interference with bile flow.

In this paper an attempt is made (1) to establish the incidence of laboratory evidence of severe interference with bile flow in primary hepatitis; (2) to analyze the results of liver function tests in cases of this disease; (3) to compare them with the results in a group of cases of extrahepatic biliary obstruction observed during the same period; (4) to establish the duration of this phenomenon; (5) to correlate it with the different types of hepatitis, and (6) to discuss the pathogenesis of this condition based on biopsy studies.

MATERIAL AND METHOD

The material of this study consists of 65 cases of proved primary hepatitis (infectious or toxic) and cirrhosis which have been examined in the past five years and in which the diagnosis was established with reasonable certainty by either subsequent course, biopsy, operation or necropsy. The results of the liver function tests on the patients' admission to the hospital were the ones taken into consideration. The presence of positive results in at least two tests for damage to hepatic cells (cephalin-cholesterol flocculation, thymol turbidity, albumin-globulin ratio, cholesterol–cholesterol ester ratio, hippuric acid synthesis, plasma

4. Watson, C. J., and Hoffbauer, F. W.: Liver Function in Hepatitis, Ann. Int. Med. **26**:813 (June) 1947.

vitamin A, nonprotein nitrogen and increased urinary urobilinogen)[5] was considered necessary for the assumption of impaired function of the hepatic cells. The second requirement in this group of cases was a positive result of at least one of the tests indicative of severe interference with bile flow (decrease of urobilinogen in feces and urine and increased serum cholesterol and serum alkaline phosphatase).

As signs of severe interference with bile flow were taken (1) a serum alkaline phosphatase level of over 15 Bodansky units, (2) a total serum cholesterol level of over 300 mg. per hundred cubic centimeters, (3) less than 1.0 mg. of urobilinogen in the urine in a twenty-four hour specimen[6] or less than ½ unit in a two hour specimen[7] and (4) less than 10 mg. of urobilinogen in 100 Gm. of stool.[8]

A phosphatase level of over 15 Bodansky units was taken as an indication of severe interference with bile flow because pathologic levels of between 4 to 15 units are too commonly found in all types of hepatitis. Obviously, a phosphatase level higher than 15 Bodansky units may be due to causes other than biliary or hepatic, but in the presence of jaundice such other causes are rarely to be considered. Similar considerations hold true also for the selection of a total serum cholesterol level of 300 mg. per hundred cubic centimeters.

In 2 cases of this series only one of the tests for impairment of hepatic function gave a positive reaction, and in 1 case no impairment was noted. In all 3 of them results of tests for severe interference with bile flow were positive. Their medical nature, however, was indicated by their history and confirmed by the subsequent course.

The entire series of 65 cases was contrasted with 46 cases in which similar results of function tests were obtained and which were observed during the same period but which proved to be cases of surgical jaundice.

RESULTS

Incidence.—During the period in which we studied the 65 cases of medical jaundice in which severe interference with bile flow was revealed at the time of admission to the hospital, 228 cases of primary hepatitis were observed. Accordingly, 28.5 per cent of cases of medical jaundice revealed severe interference with bile flow.

Analysis of Tests.—In the 65 cases of this group, usually three or four of the tests for damage to hepatic cells gave positive results

5. The pathologic levels in the various tests and the method used are described in another paper (Popper, H., and Steigmann, F.: Laboratory Tests in the Differential Diagnosis of Jaundice, Ann. Int. Med. **29**:469 [Sept.] 1948).

6. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936.

7. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: A Simple Method for the Quantitative Recording of the Ehrlich Reaction as Carried Out with Urine and Feces, Am. J. Clin. Path. **14**:605 (Dec.) 1944.

8. Steigmann, F., and Dyniewicz, J. G.: Studies of Urobilinogen: The Daily Urobilinogen Excretion in Urine and Feces in Health and Disease; An Evaluation of Watson's and Sparkman's Method, Gastroenterology **1**:743 (Aug.) 1943.

(fig. 1). The number of instances in which each of the tests indicated a pathologic condition is given in table 1. It appears from it that the cephalin-cholesterol flocculation and thymol turbidity tests, as well as the albumin-globulin ratio, most often indicated a pathologic condition, whereas the cholesterol–cholesterol ester ratio was significantly lowered in about half of the cases. In a few cases with signs of severe interference with the bile flow the urinary urobilinogen level appeared high. In them, however, the interference was manifested only by increase in the phosphatase and/or the total cholesterol.

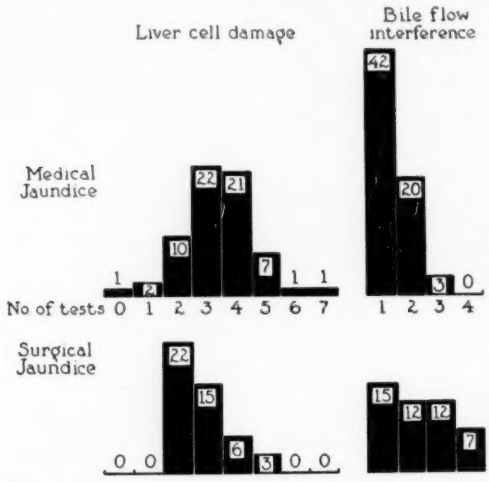

Fig. 1.—Number of patients (indicated by black column) in whom a given number of liver function tests elicited a positive reaction.

TABLE 1.—*Results of Tests for Impairment of Hepatic Function in the Presence of Severe Interference with Bile Flow and Damage to Hepatic Cells*

Type of Test *	Positive Results, Percentage	
	Medical Jaundice	Surgical Jaundice
Cephalin-cholesterol flocculation	87.6	28.0
Thymol turbidity	72.3	54.3
Albumin-globulin ratio	70.7	76.0
Cholesterol-cholesterol ester ratio	52.3	58.6
Hippuric acid excretion	21.5	28.2
Nonprotein nitrogen	15.3	21.7
Increased urinary urobilinogen	7.7	6.5

* The tests for plasma vitamin A and for retention of sulfobromophthalein, which were done only on a small number of patients, were not listed in this table.

In the great majority of cases only one of the tests indicating severe interference with bile flow gave a positive result, as seen in table 2. In two thirds of the cases absence of urinary urobilinogen was the determining factor in grouping them into this category, and in only one third was an appreciable increase in the phosphatase or total cholesterol responsible.

Comparison with Cases of Surgical Jaundice.—During the period in which the 65 cases of primary hepatitis or cirrhosis with severe interference with bile flow were observed, 46 cases of surgical jaundice were also studied in which the laboratory tests presented evidence of damage to hepatic cells in addition to severe interference with bile flow. Since these cases, at least from the laboratory standpoint, simulate the cases of primary hepatitis discussed here, they are contrasted in figure 1 and tables 1 and 2.

TABLE 2.—*Results of Tests for Severe Interference with Bile Flow in Cases in Which Both Damage to Hepatic Cells and Interference with Bile Flow Were Present*

Type of Test *	Positive Results, Percentage	
	Medical Jaundice	Surgical Jaundice
Absence of urinary urobilinogen	69.2	79.2
Alkaline phosphatase	29.2	69.5
Total cholesterol	15.3	50.0

* Fecal urobilinogen was not determined in all cases.

It is apparent that the number of tests indicating damage to hepatic cells is, on the average, smaller in the surgical group, although only cases in which at least two tests gave positive results were considered. As expected from reports in the literature [9] and our previous observations, the cephalin-cholesterol flocculation reaction was positive in only a relatively small number of cases of surgical jaundice and the thymol turbidity reaction in about half, while the other tests gave almost identical results. The difference in the number of positive reactions is therefore primarily due to the difference in the results of the first two tests.

Of the tests for severe interference with bile flow, a much higher number, on the average, elicited positive reactions among the surgical cases. This was primarily due to the high incidence of markedly increased alkaline phosphatase and total cholesterol levels.

9. Hanger, F. M.: Serologic Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin Cholesterol Emulsion, J. Clin. Investigation **18**:261 (May) 1939. Rosenberg, D. H.: The Cephalin-Cholesterol Flocculation Test in Cases of Disease of the Liver, Arch. Surg. **43**:231 (Aug.) 1941.

Type of Hepatitis.—The cases of primary hepatitis with marked interference in bile flow discussed in this paper can be divided etiologically into cases of homologous serum jaundice, infectious (viral) hepatitis, toxic hepatitis and cirrhosis. Figure 2 indicates also the additional cases of primary hepatitis without severe interference in bile flow observed during the same period. The highest incidence of this phenomenon was found in the group of cases of homologous

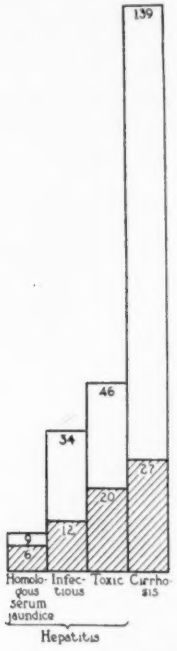

Fig. 2.—Incidence of marked interference with bile flow in the various types of hepatitis and in cirrhosis indicated by the cross-hatched columns. The total number of cases observed is indicated by the entire column.

serum jaundice (66.6 per cent). The next highest incidence was seen in cases of toxic hepatitis (43.5 per cent). It occurred in 35.3 per cent of cases of infectious hepatitis and in 19.3 per cent of the observed cases of cirrhosis.

Duration of Interference with Bile Flow.—The duration was not established in the majority of cases because daily follow-up examinations were not available. In a relatively small number of cases daily deter-

minations of urobilinogen were made which indicated the length of time during which urobilinogen was absent from the urine. In 9 of the 65 cases absence of urobilinogen from the urine persisted for three to ten days, whereas in 12 cases it persisted for over ten days. In 1 case each the phenomenon was observed for thirty-three, thirty-seven and forty-one days.

Histologic Observations.—Biopsies of material from the liver[10]—needle aspiration or surgical—were performed in some cases at a time when interference with the bile flow existed. In contrast to expectations based on a few scattered observations in the literature[11] as well as on experience from our own old material,[1b] no characteristic morphologic changes were found which differentiated the cases of primary hepatitis with severe interference in bile flow from those without it. Previously, inflammatory changes in the portal triads associated with portal fibrosis or proliferation of the bile ducts were considered responsible for the interference with the bile flow by causing compression or actual interruption of the smallest bile ducts. In some of the patients with primary hepatitis and severe interference with the bile flow, extensive infiltration by round cells and occasionally also by polymorphonuclear cells was found in the periportal fields, presenting the characteristic picture of a subacute or chronic perilymphangitis. The cellular exudate surrounded the septal bile ducts (fig. 3*A*). However, similar or even more extensive changes were found in cases of primary hepatitis without laboratory evidence of severe interference with bile flow (fig. 3*B*). Moreover, in some of the cases of acute hepatitis, even in those in which there was long duration of interference with bile flow, the described inflammatory changes were absent and the portal triads revealed no morphologically recognizable aberration from the normal. The hepatic cells were, however, loaded with bile pigment, and the bile capillaries, especially, in the center of the lobules were dilated and filled with casts (fig. 3*C*). Only in a few cases of cirrhosis was there a morphologic picture which could explain the marked interference with bile flow. Dense fibrous connective tissue encircled the smallest bile ducts and seemed to compress them, whereas the nearby bile capillaries in the periphery of the lobules appeared maximally dilated. This picture appeared to be the result of an obstruction (fig. 3*D*).

10. The aspiration biopsies were performed by Dr. D. D. Kozoll and Dr. I. Stein Jr.

11. Hanger, F. M., and Guttman, A. B.: Postarsphenamine Jaundice Apparently Due to Obstruction of Intrahepatic Bile Tract, J. A. M. A. **115**:263 (July 27) 1940. Popper.[2b]

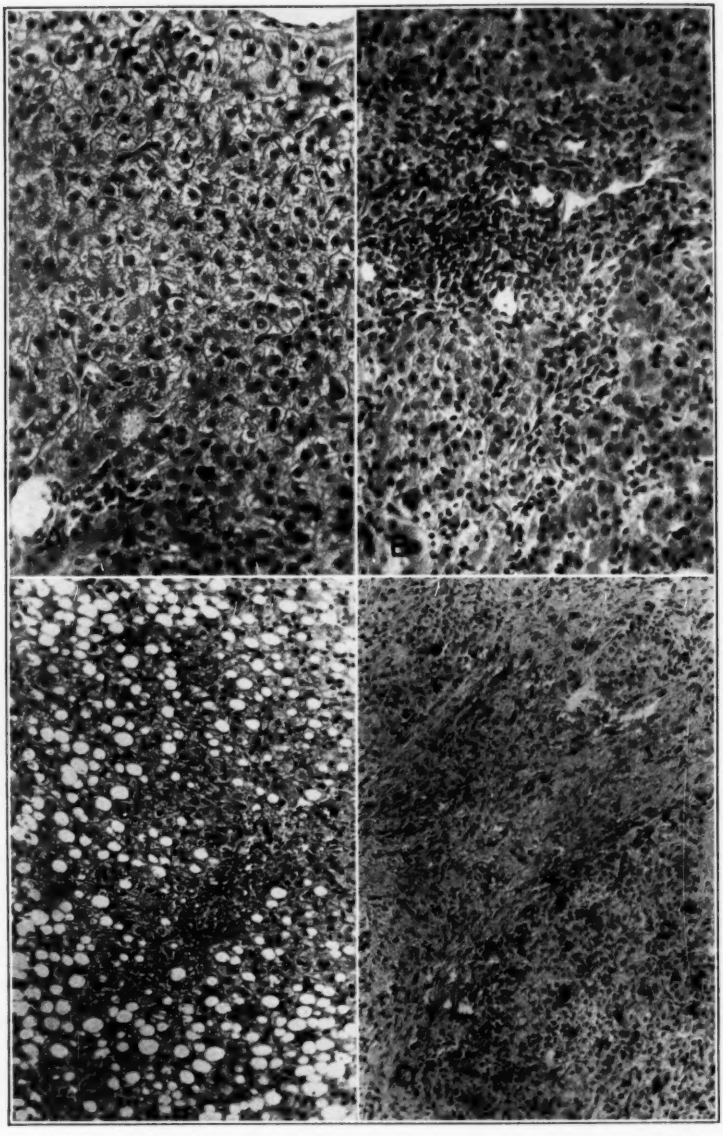

Fig. 3.—Photomicrographs of specimens of liver. *A*, acute infectious hepatitis associated with marked interference with bile flow. Moderate damage to hepatic cells, bile pigment in cells and bile casts in bile capillaries are revealed; round cellular exudate is found around septal bile ducts in a small portal triad. *B*, subacute infectious hepatitis without great interference with bile flow. There is considerable damage to hepatic cells, with regeneration. There is dense round cellular and histiocytic infiltration of the portal triads radiating into the parenchyma along septal bile ducts. *C*, toxic hepatitis of the fatty type associated with marked interference with bile flow. Much bile pigment is seen in hepatic cells. The dilated bile capillaries contain bile casts; the periportal fields are not infiltrated. *D*, portal cirrhosis associated with great interference with bile flow. The septal bile ducts in the wide connective tissue trabeculae are encircled by dense collagenous fibers, whereas the bile capillaries on the periphery of the nodules are dilated and filled with bile casts.

REPORT OF CASES

CASE 1.—A 23 year old white woman entered the hospital because of fever, coryza, headache, malaise, anorexia, nausea and vomiting. These symptoms began about two weeks after a prophylactic injection of influenza vaccine. Two and a half weeks before her admission to the hospital she noticed that her urine had become dark and her stools light, and shortly thereafter she became aware of a yellowish discoloration of her skin. The jaundice appeared to increase in severity, and swelling of her legs and dyspnea on exertion developed. The patient denied taking any medication or having been exposed to any industrial hazards. On admission she was severely jaundiced but well nourished. The abdomen was slightly distended, the liver was palpable 2 cm. below the costal margin and there was pitting edema of the legs. The urine contained bilirubin but no urobilinogen. The hemoglobin content was 55 per cent, with a red blood cell count of 3,920,000. The white blood cell count was 6,450, with 75 per cent polymorphonuclear cells, 15 per cent lymphocytes and 10 per cent monocytes. The erythrocytes showed a tendency to macrocytosis. The nonprotein nitrogen content was 25 mg. per hundred cubic centimeters, the total serum cholesterol 112 mg., with 10.7 per cent cholesterol esters, the serum alkaline phosphatase 5.6 Bodansky units, the icterus index 112, the thymol turbidity 8.6 units, the cephalin-cholesterol flocculation 4 plus and the albumin-globulin ratio 2.8 : 1.5. A diagnosis of infectious hepatitis—possibly homologous serum jaundice—was made. The patient was treated with a 4,000 calorie diet, high in carbohydrates and protein; she also received a liver preparation intravenously. Repeated examinations of urine showed bilirubin but no urobilinogen. Not until the twenty-third day after admission did a trace of urobilinogen appear in the urine. The patient had a stormy course; her abdomen became more distended, ascites developed and edema of the legs increased. However, after repeated blood transfusions and administration of vitamin preparations and amino acids she continued to improve. After thirty days repeat liver function tests showed the cephalin-cholesterol flocculation to be 4 plus, the thymol turbidity 11.6 and the total serum cholesterol 123. The cholesterol esters had increased to 55 per cent. The total serum protein, however, was still low, and the albumin-globulin ratio was reversed to 1.6 : 3.0; the alkaline serum phosphatase was 6.9 units, and the urine contained 3 units of urobilinogen. The patient continued to improve and left the hospital ninety-five days after admission.

CASE 2.—A 40 year old man entered the hospital because of jaundice of one week's duration. He had no pain but only mild nausea, weakness and slight pruritus. The stools had been clay colored for four or five days. He had been taking about 2 quarts (2,000 cc.) of beer daily for over twenty years. There had been no exposure to any hepatotoxic drugs or industrial hazards. He denied having received blood or other injections in recent months. On admission he appeared well nourished but jaundiced. The abdomen was protuberant, with the liver palpable 5 fingerbreadths, and the spleen 2 fingerbreadths below the costal margin. Ascites was present. Spider nevi were seen over the face and trunk. The urine contained bilirubin but no urobilinogen. The hemoglobin content was 67 per cent, with a red blood cell count of 3,560,000. The white blood cell count was 5,500, with 76 per cent polymorphonuclear cells, 10 per cent lymphocytes and 14 per cent monocytes; target cells were noted. The cephalin-cholesterol flocculation was 4 plus. The thymol turbidity test showed 6.4 units. The total

serum cholesterol was 475 mg. per hundred cubic centimeters, with 21 per cent cholesterol esters. The serum alkaline phosphatase was 11 Bodansky units. The albumin-globulin ratio was 3.0:3.0. A diagnosis of acute hepatic damage with intrahepatic obstruction in a patient with cirrhosis was made. The patient was put on a liver regimen, and urinary follow-up studies were made daily. On the twenty-fourth day urobilinogen appeared in the urine (2.59 mg. in twenty-four hours). At this time the cephalin-cholesterol flocculation was 4 plus and the thymol turbidity 8.6 units. The total serum cholesterol had dropped to 350 mg. per hundred cubic centimeters, the cholesterol esters had risen to 71 per cent, the serum alkaline phosphatase was 8.9 Bodansky units and the albumin-globulin ratio was 2.7:3.9. The patient improved slowly and was released from the hospital five weeks after admission.

CASE 3.—A 45 year old Negro woman entered the hospital because of anorexia, nausea, weakness and pain in the epigastrium of two weeks' duration and also jaundice and light stools for one week. Similar epigastric pain with nausea and vomiting but without jaundice had occurred two years before when she was told that her gallbladder was diseased. Since then she had occasional epigastric distress and nausea whenever she ate greasy or fried foods. There was no history indicating exposure to hepatotoxic drugs or of having received injections of any kind or blood products.

On her admission to the hospital she appeared icteric but was well developed and well nourished. Her abdomen was flat and soft, with slight tenderness in the right upper quadrant. No masses were palpable. A diagnosis of obstructive jaundice due to disease of the gallbladder was made, but the possibility of hepatitis was also considered. The urine contained bilirubin but no urobilinogen. The nonprotein nitrogen was 25 mg. per hundred cubic centimeters; the cephalin-cholesterol flocculation was 3 plus; the thymol turbidity was 13.2 units; the icterus index was 151; the albumin-globulin ratio was 2.8:2.8; the serum alkaline phosphatase was 3.9 Bodansky units, and the total serum cholesterol was 253 mg. per hundred cubic centimeters. Hematologic examination revealed slight anemia and macrocytosis, with a white blood cell count of 9,150 and 75 per cent polymorphonuclear cells. Because of the absence of urobilinogen from the urine and the rising icterus index (151 to 174) and because of her history, she was transferred to a surgical ward for an exploratory operation. At laparotomy the liver was found to be small and hard; the gallbladder and the common duct were not distended, and no stones were found anywhere. The surgeon's impression was that the patient had a cirrhotic liver. The common duct was drained. After operation she had a stormy course but improved gradually, and nineteen days postoperatively the cephalin-cholesterol flocculation was 2 plus; the thymol turbidity 3.0 units; the icterus index 61; the albumin-globulin ratio 3.0:1.9; the alkaline serum phosphatase 3.0 Bodansky units; the total serum cholesterol 206 mg. per hundred cubic centimeters; the cholesterol esters 61 per cent; the urine urobilinogen 58.32 mg. in twenty-four hours, and the stool urobilinogen 59.2 mg. per hundred cubic centimeters. The patient left the hospital seven weeks after operation. Follow-up examination three months later showed an albumin-globulin ratio of 4.1:3.2; a total serum cholesterol level of 357, with 67 per cent cholesterol esters; a thymol turbidity of 8.6 units; a total bilirubin level of 1.6 mg. per hundred cubic centimeters; normal cephalin-cholesterol flocculation, and normal stool and urine urobilinogen levels.

COMMENT

The occurrence of severe interference with bile flow in medical jaundice is obviously of importance in the differential diagnosis, because it may suggest an extrahepatic mechanical origin of the jaundice, which therefore would require operation. A survey of a large number of cases of jaundice due to established primary hepatitis or cirrhosis revealed that in such cases severe interference with bile flow is not uncommon. It occurred approximately in one fourth of the cases if one took the first complete laboratory examination into account. At times it was rather persistent, although the material presented here does not permit statements as to the duration in most cases.

From the laboratory standpoint this group is almost identical with the large group of cases of surgical jaundice in which damage to hepatic cells is present. Obviously, clinical observation based on an exact history and clinical findings will often permit the differentiation. However, laboratory examinations are of some, though limited value. As a rule, more tests for damage to hepatic cells and less tests for severe interference with bile flow give positive results in the medical group. In the latter the reaction to the cephalin flocculation test is far more often positive, less so the reaction to the thymol turbidity test, whereas the other tests fail to show much difference in the results. On the other hand, the alkaline phosphatase is markedly increased (above 15 Bodansky units) and the total cholesterol is above 300 mg. per hundred cubic centimeters more often in the surgical cases than in the medical cases. On the average, therefore, severe interference with bile flow is less conspicuous in medical jaundice and impairment of hepatic function is less marked in surgical jaundice. In the individual case this relation is not always borne out, a fact which calls for alertness in the interpretation of the tests of function.

It is of considerable interest that the incidence of this phenomenon varies in the different types of hepatitis. Recently, based on morphologic examination, the difference between infectious (viral) and toxic hepatitis (including various known and unknown toxic agents) has been emphasized.[12] If the cases of infectious hepatitis, including homologous serum jaundice, from our material are contrasted with those of toxic hepatitis, the incidence of severe interference with bile flow is about identical, namely 41.8 versus 43.5 per cent. However, if the patients with homologous serum jaundice are taken as a separate group, an unusually high incidence of severe interference with bile flow is found, if one is permitted to draw conclusions from this small group. In contrast,

12. Popper, H., and Franklin, M.: Differential Diagnosis of Hepatitis by Histologic and Functional Laboratory Methods, J. A. M. A. **137**:230 (May 15) 1948.

the patients with infectious (viral) hepatitis, which is transmitted by the oral route, show this phenomenon less often than those with toxic hepatitis. This points to a difference between viral hepatitis and homologous serum jaundice,[13] which is in keeping with the observation that the latter is, as a rule, the more severe disease.[14] Obviously the presented breakdown of the cases is only suggestive and not established; previous exposure to blood products does not definitely prove homologous serum jaundice as a cause of the hepatitis. In the group of cases of infectious hepatitis, the diagnosis remains assumptive without demonstration of the virus or a clearcut epidemiologic background. In contrast to acute hepatitis, the phenomenon of severe interference with bile flow is far less common in cirrhosis with jaundice.

Little can be added to the understanding of the pathogenesis of this phenomenon except to withdraw statements previously made.[1b] Only in some cases of cirrhosis is a characteristic morphologic picture associated with the phenomenon, namely, when there is an encircling fibrosis obstructing the septal bile ducts. It apparently accounts for the cholostatic phase in cirrhosis. In acute hepatitis no characteristic morphologic changes can be associated with this phenomenon. A study of a larger number of cases did not confirm the previously made assumption that inflammatory changes in the periportal fields are responsible for it. At the present stage of our knowledge the explanation proposed by Watson and Hoffbauer,[3] namely, backflow of bile through anatomically unchanged cholangioles, can be accepted. Therefore one may be justified in the use of cholangiolitis as a descriptive term for this phenomenon.

It is questionable whether the higher incidence of severe interference with bile flow in the cases of homologous serum jaundice is an expression of a greater severity of the hepatitis in general or whether this disease is associated with a more marked involvement of the smallest bile ducts, cholangioles, than the other types of hepatitis. The second possibility might be explained by a greater affinity of the homologous serum virus for the cholangioles.

SUMMARY

Severe interference with bile flow as indicated by absence of urobilinogen from the urine and feces or markedly increased levels of serum alkaline phosphatase and total cholesterol was found in 28.5 per cent of cases of medical jaundice (primary hepatitis or cirrhosis).

13. Neefe, J. R.: Recent Advances in the Knowledge of "Virus Hepatitis," M. Clin. North America **30**:1407 (Nov.) 1946.

14. Lucke, B., and Mallory, T.: The Fulminant Form of Epidemic Hepatitis, Am. J. Path. **22**:867 (Sept.) 1946.

In order of decreasing incidence, this phenomenon was found in homologous serum jaundice, toxic hepatitis, infectious (viral) hepatitis and cirrhosis. In contrast to cases of surgical jaundice with damage to hepatic cells, tests indicated impairment of hepatic function more often and severe interference with bile flow less often in this group. The reaction to the cephalin-cholesterol flocculation test was far more often positive and the serum alkaline phosphatase and total cholesterol levels were less often markedly increased in the medical cases than in the surgical cases. A characteristic morphologic picture was present in some cases of cirrhosis, whereas in cases of acute hepatitis no correlation of severe interference in bile flow with anatomic changes was found. The importance of severe interference with bile flow (which is usually considered a characteristic of extrahepatic mechanical obstruction requiring surgical intervention) in the differential diagnosis of jaundice is emphasized.

SUBMUCOUS LIPOMAS OF THE COLON

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FOR MANY years surgeons have been unusually interested in submucous lipomas of the gastrointestinal tract because of their rarity, bizarre symptomatology, difficulty of diagnosis and the good prognosis after resection.

Submucous lipomas have been found along the gastrointestinal tract from the hypopharynx to the rectum. When found in the stomach or small bowel they are usually small and rarely cause symptoms. The colon has the highest incidence of submucous lipomas, and here they sometimes become bulky and cause obstruction. Of the benign tumors of the intestinal tract, lipomas are second in frequency to adenomatous polyps.

The last survey of the literature was made by Gault and Kaplan [1] in 1941, and, including their cases, there were only 130 cases of submucous lipoma of the colon reported. Of these, 111 were clinical cases and the rest were found at autopsy. Since their summary, cases have been reported by Lazarus and Marks,[2] Browne and McHardy,[3] Saint,[4] Barnes and Barnes,[5] Cooper,[6] Moore,[7] Meigs,[8] Anderson and

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1. Gault, T., and Kaplan, P.: Submucous Lipoma of the Colon, Am. J. Surg. **53**:145 (July) 1941.

2. Lazarus, A., and Marks, M.: Submucous Lipomas of Colon with Special Reference to Acute and Chronic Intussusception, Am. J. Surg. **70**:114 (Oct.) 1945.

3. Browne, D. C., and McHardy, G.: Submucosal Colon Lipomas, Clinics **3**:622 (Oct.) 1944.

4. Saint, J. H.: Chronic Intussusception Due to Submucous Lipoma of Ascending Colon, Am. J. Surg. **58**:414 (Dec.) 1942.

5. Barnes, F. L., and Barnes, J. P.: Lipoma of the Colon, South. Surgeon **9**:853 (Dec.) 1940.

6. Cooper, H. G. N.: Intussusception in an Adult Due to a Lipoma, Brit. M. J. **1**:328 (Feb. 18) 1939.

(Footnotes continued on next page)

Fansler,[9] Clagett,[10] Didier,[11] Morton,[12] Spatolisano[13] and Pack and Booher.[14] Now about 155 cases have been reported in the literature.

Staemmler,[15] Comfort[16] and Kirshbaum[17] reported an incidence of submucous lipomas of the gastrointestinal tract at autopsy varying from 0.05 to 0.6 per cent. At this hospital Humphreys,[18] in reviewing 3,100 consecutive autopsies, found 23 cases in which there were submucous lipomas of the gastrointestinal tract—an incidence of 0.75 per cent. In 15 of this group the lipomas were located in the colon (65 per cent). In 9,648 autopsies of Comfort and Kirshbaum only 13 colonic submucous lipomas were found.

The surgical services of the Albert Merritt Billings Memorial Hospital of the University of Chicago Clinics in the past eleven years have had 7 cases of submucous lipomas of the colon. Six of these cases were of clinical significance, and in the other the lipoma was an incidental finding in a colon resected for carcinoma.[19] Since most reports in the literature have dealt with single cases, we feel that a series of this size is worth reviewing.

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7. Moore, E. C.: Obstructive Submucous Lipoma of the Cecum, California & West. Med. **60**:21 (Jan.) 1944.

8. Mallory, T. B.: Case Records of the Massachusetts General Hospital: Meig's Case 27042, New England J. Med. **224**:168 (Jan. 23) 1941.

9. Anderson and Fansler: Submucous Lipomas of the Rectum, Lancet **59**:4 (Jan.) 1939.

10. Clagett, O. T.: Lipoma of Cecum, Proc. Staff Meet., Mayo Clinic **14**:505 (Aug.) 1939.

11. Didier, R.: Submucous Lipomas of the Cecum, Two Cases, Arch. d. mal. de l'app. digestif. **28**:1070 (Dec.) 1938.

12. Morton: Submucous Lipomas of the Colon, Bull. Vancouver M. A. **16**:287 (July) 1940.

13. Spatolisano, B.: A Case of Lipoma of the Descending Colon, Rassegna internaz. clin. e terap. **27**:45, 1947.

14. Pack, G. T., and Booher, R. J.: Intussuscepting Submucous Lipoma of the Right Colon, S. Clin. North America **27**:361, 1947.

15. Staemmler, M.: Das Lipom in die Neubildungen des Darmes, Stuttgart, Ferdinand Enke, 1924, pt. 1, p. 273.

16. Comfort, M. W.: Submucous Lipoma of the Gastrointestinal Tract with a Report of Twenty-Eight Cases, Surg. Gynec. & Obst. **52**:108, 1931.

17. Kirshbaum, J. D.: Submucous Lipomas of the Intestinal Tract as a Cause for Intestinal Obstruction, Ann. Surg. **101**:734, 1935.

18. Humphreys, E.: Personal communication to the authors.

19. L. N. (case 7), a 60 year old housewife, was operated on Dec. 18, 1946, and a carcinoma of the ascending colon was found. As no distant metastasis had

(*Footnotes continued on next page*)

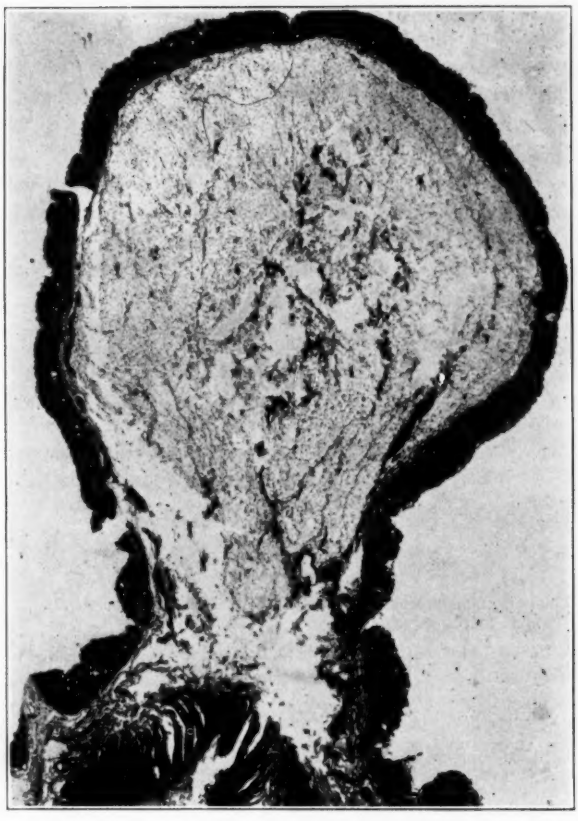

Fig. 1.—Low power photomicrograph of the 1.5 cm. submucous lipoma found incidentally in the surgical specimen of case 7.

occurred, a colectomy was performed on the right side. Examination of the specimen revealed a napkin ring constricting ulcerated carcinoma 14 cm. above the ileocecal valve. As an incidental finding 2 cm. above the ileocecal valve there was a soft fluctuant pedunculated mucosal nodule 1.5 cm. in diameter. Microscopic examination of this showed it to be a benign nonulcerated submucosal lipoma (fig. 1).

REPORT OF CASES

CASE 1.[20]—A. G., a 59 year old housewife, was subjected to a Mikulicz resection of a portion of the sigmoid colon for adenocarcinoma in 1930. She was free of symptoms for nearly six years, when suddenly she had a moderate rectal hemorrhage. A year later, on Sept. 29, 1937, she came to the surgical clinic complaining of chronic constipation and of cramping pain in the lower abdominal region associated with nausea and small bloody stools during the past week.

Physical and laboratory examinations were essentially noncontributory. Fluoroscopy of the colon and roentgenograms demonstrated a polypoid tumor 5 by 7 cm. on the anterior wall of the transverse colon (fig. 2). This mass did not obstruct the lumen and was benign in the opinion of the examiner.

Fig. 2.—Roentgenogram of the colon in case 1, reported as showing a benign tumor mass 5 by 7 cm. arising from the inferior wall of the transverse colon and projecting into the lumen.

On Oct. 25, 1937, a laparotomy was performed and a submucous lipoma of the transverse colon was found. There was no evidence of recurrence of the sigmoid carcinoma. A Mikulicz resection of the tumor-containing segment of transverse colon was performed. The postoperative course was uneventful, and closure of the colostomy opening was carried out six weeks later.

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20. This case was reported by Dr. O. C. Julian in the April 1939 issue of Radiology.

The pathologic specimen consisted of a 5.5 cm. segment of colon containing a pedunculated soft yellow submucous tumor measuring 7.5 by 4.5 by 4.0 cm. The mass was freely movable beneath the intact mucosa and when cut was obviously a lobulated fatty tumor. Microscopic sections confirmed the diagnosis of lipoma (fig. 3).

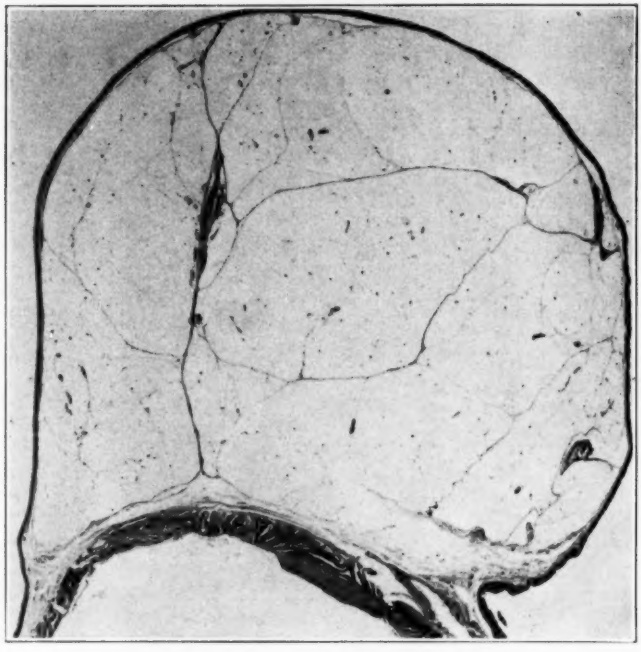

Fig. 3. —Low power photomicrograph of the resected colon and submucous lipoma in case 1.

CASE 2.—M. D., a 51 year old housewife, was seen in the surgical clinic on Nov. 6, 1940, complaining of cramping pain in the lower abdominal region increasing in frequency and severity for six weeks and relieved by bowel movements. She had lost 20 pounds (9.1 Kg.) of weight during this period and felt weak. She had noticed increasing difficulty in moving her bowels, and her stools were poorly formed and watery and contained a great deal of mucus.

Physical examination showed an anxious woman with evidence of recent loss of weight. A tender, smooth, movable mass 3 by 5 cm. was palpable at the level of the left iliac crest. Roentgenograms of the colon showed a 4 cm. polypoid mass almost filling the lumen of the distal part of the transverse colon. The

examiner was unable to differentiate between a benign or malignant lesion but favored the former. Mild anemia was present.

On Nov. 12, 1940, operation was performed and exploration revealed a mass in the region of the splenic flexure believed to be a papilloma or lipoma. A Mikulicz obstructive type of resection was carried out, a segment of the colon including the tumor being removed. Eleven weeks later the colostomy opening was closed.

Examination of the specimen revealed in the resected segment of colon a polypoid submucous tumor 3.5 cm. in diameter. The distal portion of the tumor, consisting of lobulated fat, was not covered by mucosa (fig. 4). Microscopic examination confirmed the gross impression of an ulcerated submucosal lipoma.

Fig. 4.—Photograph of the resected colon showing the polypoid submucous lipoma in case 2. The mucosa is absent over part of the surface exposing the lobulated fat of the tumor.

CASE 3.—S. T., a 40 year old housewife, was first seen on Nov. 20, 1942, in the gastrointestinal clinic complaining of attacks of cramping pain in the upper abdominal area present for five to seven years and relieved by loose bowel movements. Twice in the previous two and one-half months she had noted bright red blood with defecation. These attacks had become worse during the past year but were alternated with periods in which she was free from symptoms. She had lost 32 pounds (14.5 Kg.) over the past five years. Roentgenograms of the gastrointestinal tract taken in 1940 had been reported as normal. In 1942 roentgenograms of the colon were first reported as normal, but a narrowing and peculiar configuration of the mucosal pattern seen in the ascending colon led to reexamination. The findings were still indeterminate, as the deformities could

be explained on the basis of accumulated gas and fecal material. Stools contained occult blood. Slight anemia was present. The patient was started on a regimen for functional bowel distress, with temporary improvement. She was seen repeatedly over the next eight months, and when her cramping abdominal pain persisted roentgenograms were again made. On Aug. 13, 1943, fluoros-

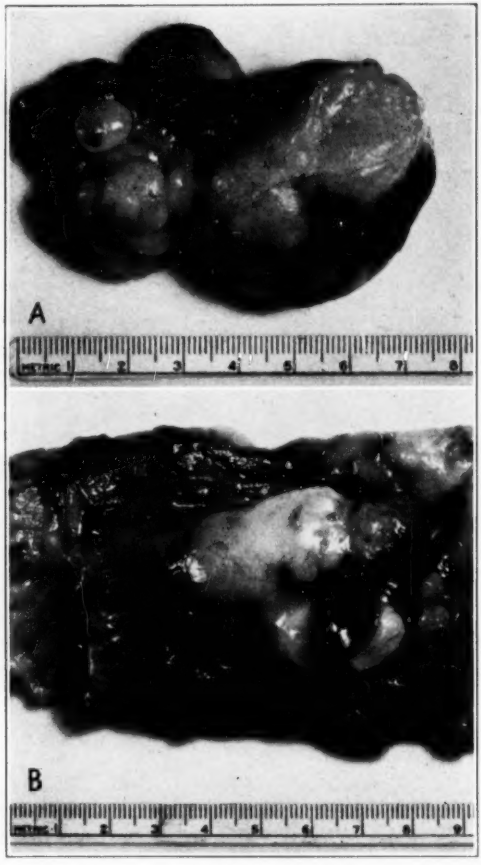

Fig. 5.—*A*, photograph of the lobulated submucous lipoma removed by local excision from the cecum in case 3. *B*, photograph of the resected segment of colon containing the lobulated polypoid submucous lipoma in case 4.

copy revealed a polypoid tumor in the ascending colon causing transitory obstruction.

On August 26 an exploratory laparotomy was performed and a mass palpated in the region of the hepatic flexure which had caused intussusception of the

ascending colon. It was possible to reduce the intussusception, and a 5 to 6 cm. tumor was found apparently attached by a long pedicle to the cecum. The cecum was opened, and the tumor, a lipoma, was removed by cutting the pedicle. The stalk was infolded by two layers of sutures, and the cecum was closed. The resected pedunculated tumor, 6 by 4.5 by 4 cm., weighed 47 Gm. (fig. 5 *A*). There was no ulceration or necrosis grossly, and on cut section the mass appeared to be adipose tissue. The pathologic diagnosis was a nonulcerated submucous lipoma of the colon.

Case 4.—G. B., a 46 year old man, was first seen on Aug. 18, 1943, complaining of transient attacks of watery blood-tinged stools six to seven times daily for one and one-half years. The associated mild pain in the left flank was relieved by bowel movements. There was increased rumbling and abdominal distention. Roentgenograms of the gastrointestinal tract taken early in the course of his illness were reported as normal, and he was placed on a bland diet with only temporary relief. There was a marked recurrence of symptoms six months before his visit to the clinic.

Abdominal examination failed to reveal any palpable masses but hyperactive peristalsis was noted. Roentgenologic examination revealed a polypoid lesion at the junction of the descending and sigmoid colons interpreted as a carcinoma.

On August 27 a laparotomy was performed and a pedunculated 3 to 4 cm. yellow tumor of the sigmoid colon, believed to be a lipoma, was found. An obstructive Mikulicz type of resection of the segment of bowel containing the tumor was carried out. Three weeks later the colostomy opening was closed.

Examination of the specimen revealed an 8 cm. segment of sigmoid colon containing a polypoid tumor 3.5 by 4 by 3 cm. on the antimesenteric border (fig. 5 *B*). The mucosa was smooth and intact over the tumor. Cut section of the mass showed it to be made of lobulated fat tissue. Microscopic sections confirmed the diagnosis of a nonulcerated submucous lipoma of the colon.

Case 5.—H. M., a 57 year old man, was seen on Dec. 14, 1945, complaining of cramping pain in the lower abdominal area present for seven months. These attacks of pain, lasting fifteen to sixty minutes, occurred chiefly before meals or at bedtime and were relieved by a bowel movement or by passing flatus. For two or three months he had had diarrhea, and on several occasions he had passed blood. He had lost 15 pounds (6.8 Kg.) of weight during the past six months.

It may be significant that this patient had been seen in 1929 in the Medical Clinic of this hospital with similar complaints. All examinations were noncontributory, and a diagnosis of functional bowel distress had been made.

Physical examination revealed a movable 8 to 10 cm. mass to the right of the umbilicus. Roentgenograms of the colon showed a large mass in the cecum reported to be either a carcinoma or a benign tumor such as a lipoma. The tendency of this lesion to intussuscept into the ascending colon was noted at fluoroscopy.

A laparotomy was performed on Dec. 21, 1945. After dense adhesions in the right lower quadrant were freed, a mass was found in the ascending colon. In the belief that it was a carcinoma, a colectomy, with a side to side ileotransverse colostomy, was performed on the right side.

The specimen consisted of the right colon containing an ulcerated sessile mass 3 by 4 by 3.5 cm. located 2 cm. distal to the ileocecal valve (fig. 6). On cut section the mass was found to be made up of soft cystic fatty tissue. On microscopic examination it proved to be a submucosal lipoma with an ulcerated infected surface (fig. 7).

Fig. 6. —Photograph of the resected portion of the cecum in case 5 showing the polypoid submucous lipoma with an ulcerated surface.

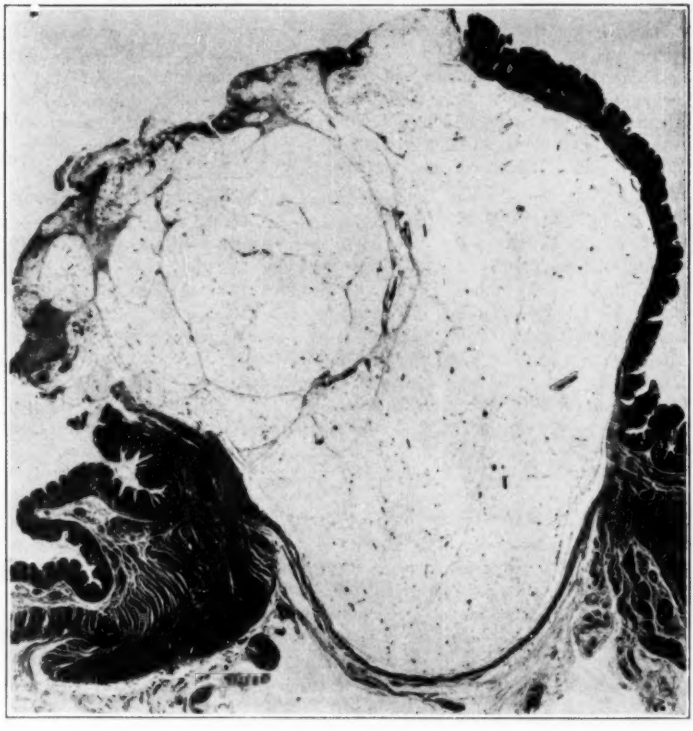

Fig. 7.—Low power photomicrograph of the submucous lipoma with an ulcerated surface removed in case 5.

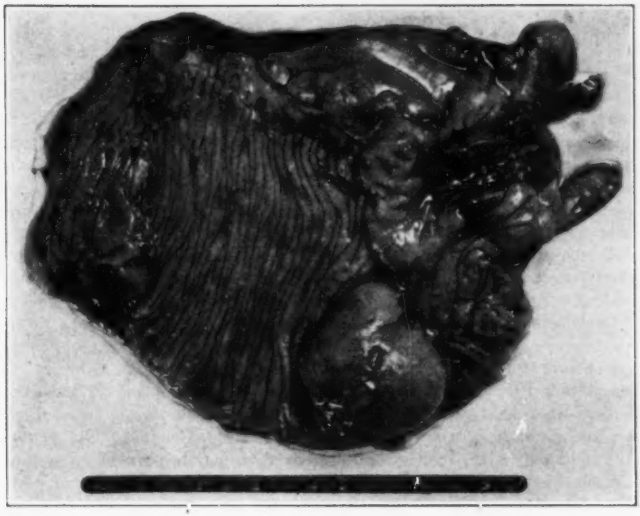

Fig. 8.—Photograph of the resected colon in case 6 showing the submucous lipoma.

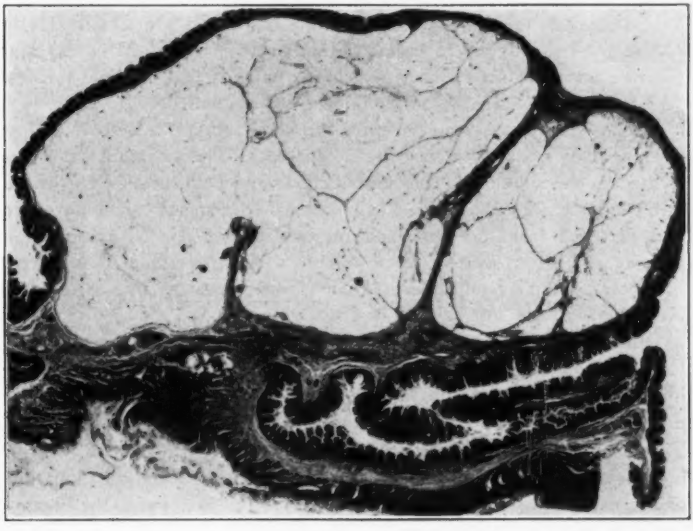

Fig. 9.—A low power photomicrograph of the colon in case 6 containing a submucous lipoma. There is some loss of mucous membrane over part of the tumor.

CASE 6.—J. N., a 57 year old housewife, complained of constipation and sharp stabbing abdominal pain in 1930. A diagnosis of functional colitis was made, and she was treated with a bland diet, with improvement. Roentgenograms of the colon in 1943 were normal.

This patient was next seen in the Surgical Clinic on March 14, 1947, complaining of increasing constipation for six weeks, associated with epigastric cramping pains, anorexia and weakness. One week before entering this hospital a barium enema revealed an intussusception of the ascending colon. This was reduced, and a filling defect in the right side of the colon was demonstrated.

Physical examination revealed a soft flabby abdomen with a large tubular tender smooth mass 10 by 4 cm. on the right side. Roentgenograms of the colon showed intussusception of the terminal portion of the ileum and cecum into the ascending colon. When this was reduced a mass was present in the cecum.

The patient was operated on on March 18, 1947, with a preoperative diagnosis of carcinoma of the cecum. A globular mass was felt in the cecum, and under direct observation the cecum intussuscepted several times into the ascending colon. After palpation it was felt that the lesion was a benign lipoma. Local excision was considered but was decided against because of the sessile nature of the lesion and its close proximity to the ileocecal valve. Colectomy was performed on the right side, a side to side ileotransverse colostomy being used.

Examination of the specimen revealed a 6 cm. polypoid yellow tumor of the cecum covered by intact mucosa (fig. 8). On cut section it was made up of lobulated fat—a typical submucous lipoma of the cecum (fig. 9).

COMMENT

Submucous lipomas of the gastrointestinal tract are usually single although Comfort's [16] (13 cases), Humphreys' [18] (4 of 23 cases) and Browne and McHardy's (a recent case) patients had multiple tumors. In 7 cases of this series a single lipoma was present.

Apparently there is no tendency for these tumors to become malignant. They are highly vascular lobulated masses of adult fat cells, located in the submucosa and extending as polypoid or sessile growths into the lumen of the bowel. Their mucosal covering is usually atrophic and flattened from pressure and may be ulcerated. Ulceration was present in 2 of our cases. These tumors vary in size from 1 to 12 cm. in diameter and average about 4 cm. The largest in this series was 6 cm. and the smallest 1.5 cm. in diameter.

Since these lipomas tend to become polypoid, they have a tendency to be pulled out on a long stalk by the peristaltic activity of the intestine. This may result in a dimpling of the serosa at the base of the tumor, a characteristic sometimes seen with other large polypi. This dimpling was not noticed in any of the cases of this series. Large lipomas sometimes show hemorrhage, cystic degeneration, inflammation or necrosis. The only change of this type in this series was the inflammation present in the 2 cases of ulceration.

The order of frequency of the location of these tumors is usually given as cecum, ascending colon, sigmoid colon, transverse colon,

rectum and descending colon, with a preponderance on the right side. In our group one tumor was in the cecum, two were just distal to the ileocecal valve and one each was found at the splenic flexure, in the ascending colon, in the transverse colon and in the sigmoid colon.

In this series the ages varied from 40 to 60, with an average of 53. There were 5 women and 2 men. These figures parallel the age incidence and sex ratio given by Pemberton and McCormack.[21] The duration of symptoms in this group varied from six weeks to six or seven years, with the majority a year or over.

The usual signs and symptoms of submucous lipomas of the colon are not pathognomonic. They are colicky abdominal pain, a palpable tumor, constipation, loss of weight, rectal bleeding and anemia. All our patients with clinically significant symptoms (excluding case 7) reported cramping abdominal pain. Only 3 had a palpable tumor. When a mass is palpated it can be the lipoma itself, fecal material dammed back by the tumor or intussuscepted bowel. Four of our patients reported constipation and 4 at some time had loose stools. Three reported an appreciable loss of weight. Six reported rectal bleeding, but in only 2 cases was it severe enough to cause anemia.

Submucous lipomas may produce three complications—obstruction, intussusception and hemorrhage. All our patients had some degree of obstruction. Intussusception was present in 3 cases, as shown by roentgenograms or during operation. This parallels the 40 to 45 per cent incidence of intussusception reported in the literature. Strangulation with sloughing and spontaneous expulsion of the lipoma through the rectum have been reported in 20 cases. Two of the more recent cases have been reported by Manheim and Peskin [22] and Backenstoe.[23] Rectal bleeding was present in 6 cases. This may be caused by trauma to the tumor caused by fecal material or intestinal motility, by erosion of the mucosa of the tumor, by pressure ulceration of the mucosa opposite the tumor as reported by Saint [4] or by intussusception.

Most writers report two symptom complexes associated with these tumors. One is a chronic course, often years long, of gradually increasing intermittent obstruction. The other is an acute course lasting a few hours or days and terminating in intestinal obstruction which is often precipitated by intussusception. Although intussusception was demonstrated in 3 cases in this group, there were no cases of acute obstruction. The intussusceptions were of the type which recurred and reduced spontaneously.

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21. Pemberton, J. De J., and McCormack, C. J.: Submucous Lipomas of the Colon and Rectum, Am. J. Surg. **37**:205, 1937.

22. Manheim, S. D., and Peskin, H.: Spontaneous Elimination of a Lipoma from the Sigmoid Flexure, J. A. M. A. **118**:1214 (April 4) 1942.

23. Backenstoe, G. S.: Spontaneous Expulsion of Submucous Lipoma of Cecum, Pennsylvania M. J. **44**:21 (Oct.) 1940.

Summary of Case Reports of Colonic Submucosal Lipomas

	1	2	3	4	5	6
Age	50	51	40	46	57	57
Sex	F	F	F	M	M	F
Duration of symptoms	1 yr.	6 wk.	6 to 7 yr.	1½ yr.	7 mo. (possibly 7 yr.)	6 wk. (possibly 15 yr.)
Constipation	+	+	0	0	+	+
Diarrhea	0	+	+	+	+	0
Melena	+	+	+	+	+	+
Cramping abdominal pain	+	+	+	+	+	+
Anemia	0	+	+	0	0	0
Weight loss, lb	0	20 (9.1 Kg.)	32 (14.5 Kg.)	0	15 (6.8 Kg.)	2 (0.9 Kg.)
Palpable mass	0	+	0	0	+	+
Roentgen diagnosis	Polypoid benign tumor; no obstruction	Polypoid mass (benign or malignant?)	Polypoid tumor	Polypoid lesion, probably malignant but has benign features	Polypoid mass, carcinoma or benign tumor	Organic mass
Location	Transverse colon	Splenic flexure	Ascending colon	Junction of descending colon and sigmoid	Ascending colon	Cecum
Intussusception	0	0	+	0	+	+
Operation	Modified Mikulicz, obstructive resection	Modified Mikulicz, obstructive resection and cholecystectomy	Local excision	Modified Mikulicz, obstructive resection	Colectomy on right side	Colectomy on right side
Size	7.5 × 4.5 × 4.0 cm.	3.5 × 3.5 × 3.5 cm.	6 × 4.5 × 4 cm. (Weight, 47 Gm.)	3.5 × 4.0 × 3.0 cm.	3 × 4 × 3.5 cm.	6 × 6 × 6 cm.

The absence of acute cases probably in part accounted for the absence of mortality in this group of cases. Lazarus and Marks [2] reported a mortality of 11 per cent in the series they reviewed. There were no postoperative complications in the present series.

It is interesting to note that the diagnosis of submucous lipoma of the colon was appreciated at the operating table in 5 of the cases. One was resected in the belief that it was a carcinoma.

With increased experience, the roentgenologists have in many instances been able definitely to make a diagnosis of a benign tumor of the colon in these cases. If the lipoma is of sufficient size, in mucosal relief roentgenograms it often shows up as a radiolucent area. In 2 of our cases the roentgenologist suggested the diagnosis of benign tumor, probably a lipoma. In 3 other cases there were findings suggestive of the possible benign nature of the lesion—movable circumscribed sessile or polypoid tumors in a pliable undeformed bowel. Careful roentgenologic examination of the lesion can, at least in many instances, alert the surgeon to the possibility of the tumor being benign.

Cases 1 and 7 are of considerable interest for the association of the submucous lipomas with carcinoma. In case 1 the patient had undergone a successful resection of a carcinoma of the sigmoid colon seven and one-half years before. She had symptoms of a similar condition on her later admission to the hospital, but exploration showed no recurrence of carcinoma and a submucous lipoma of the transverse colon was resected. In case 7 a preoperative diagnosis of carcinoma of the transverse colon was made, and at operation a carcinoma of the hepatic flexure was found. As an incidental finding a small submucous lipoma was found in the cecum. In the absence of the carcinoma this lipoma could well have passed unnoticed.

Submucous lipomas in our series were treated by three different operations, depending on the diagnosis at the operating table, location and size. One lipoma in the ascending colon was removed at the base of its pedicle. Three lipomas located in the transverse colon, splenic flexure and descending colon were removed by a modified obstructive type of Mikulicz resection. Two tumors in the right side of the colon were removed by means of colectomy.

With improvements in roentgenologic technic and interpretation, the preoperative diagnosis of these tumors becomes a distinct possibility. In a majority of cases evidence suggestive of the benign nature of the lesions can be found during fluoroscopy of the colon. With the possibility of the lesion being a benign lipoma in mind, the surgeon should be able to recognize the lesion at the operating table in a high percentage of cases. The yellow color of the tumors, their pedunculated nature, the dimpling of the serosa at the base of the pedicle, their elasticity on palpation, the absence of infiltration at the base and the absence of

local or distant metastasis will usually allow the surgeon to make the diagnosis. If he is still uncertain, there is no contraindication to opening the bowel for more direct observation of the tumor.

When the diagnosis is made, local resection by enucleation of the tumor or by cutting the pedicle is the operation of choice. There are a few cases in which a local resection of the bowel with end to end anastomosis will be necessary. There is little danger of local recurrence or malignant degeneration of these tumors, so more radical resections are not necessary.

SUMMARY

1. Six cases of surgically significant submucous lipoma of the colon and 1 case in which the lipoma was an incidental finding after a resection of the colon for carcinoma are reviewed.

2. A discussion of the frequency, location, symptoms, physical findings, roentgenologic diagnosis and treatment is presented.

3. Recognition of the lesions at the operating table with more consecutive excisions and consequent reduced mortality and morbidity rates is believed to be the desired trend in the management of these lesions.

PRESERVATION OF THE ANAL SPHINCTER IN SURGICAL PROCEDURES IN THE RECTOSIGMOID REGION

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WASHINGTON, D. C.

IN RESECTION of the rectosigmoid region for carcinoma, it has been the practice of a large group of surgeons to remove the anus and the sphincter, substituting a colostomy opening; a smaller, but perhaps no less vocal, group believes that the sphincter can be retained without the penalty of a higher immediate or remote mortality. This amiable feud goes on and on, with concessions from either side, and in all fairness it can be said that both groups have honest convictions. I believe there is enough information available concerning many aspects of the subject to permit some rational decision.

Two questions naturally arise: First, is it possible to retain a functioning anal sphincter without materially increasing the risk of operation and, at the same time, maintain a record of five year cures comparable to that of the colostomizing operation? Second, can the operation be done with the assurance that a normally functioning sphincter will remain?

The abdominoperineal resectionists are responsible for the statement or general impression that only by removing the entire distal end of the gastrointestinal tract can one minimize recurrences of carcinoma. The point is emphasized that by removal of the sphincter and sections of the levator muscles, the path of metastasis is interrupted or obliterated: a colostomy is a necessary by-product. Glover and Waugh [1] have shed much light on the subject of metastasis in carcinoma of the rectum and sigmoid. I believe that no other contribution in recent years has approached the thoroughness of their work, which upsets some generally accepted theories concerning the secondary distribution of cancer in this region.

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1. Glover, R. P., and Waugh, J. M.; The Retrograde Lymphatic Spread of Carcinoma of the Recto-Sigmoid Region, Surg., Gynec. & Obst. **82**:434-448 (April) 1946.

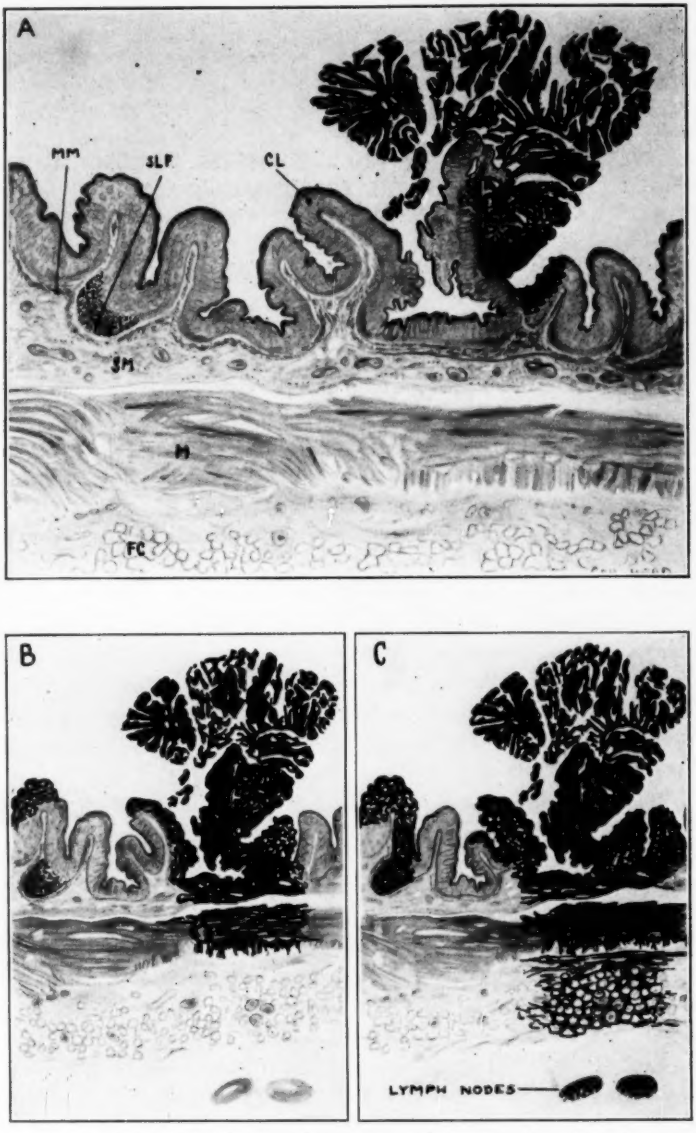

Fig. 1.—Duke's classification of carcinoma of the rectosigmoid: *A*, tumor limited to the wall of the rectum; *B*, spread by continuity to the extrarectal tissues, but not to the regional nodes; *C*, metastasis present in the regional nodes. *MM* indicates muscularis mucosae; *SLF*, single lymph follicle; *CL*, crypt of Lieberkühn; *SM*, submucosa; *M*, muscle, and *FC*, fat cells.

In 100 cases of resection of the rectosigmoid region for carcinoma, Glover and Waugh meticulously went through the operative histories and the pathologic sections. In 20 per cent of the cases carcinoma had spread to the liver by way of the venous channels. In less than 1 per cent were nodes involved more than 2 cm. below the margin of the

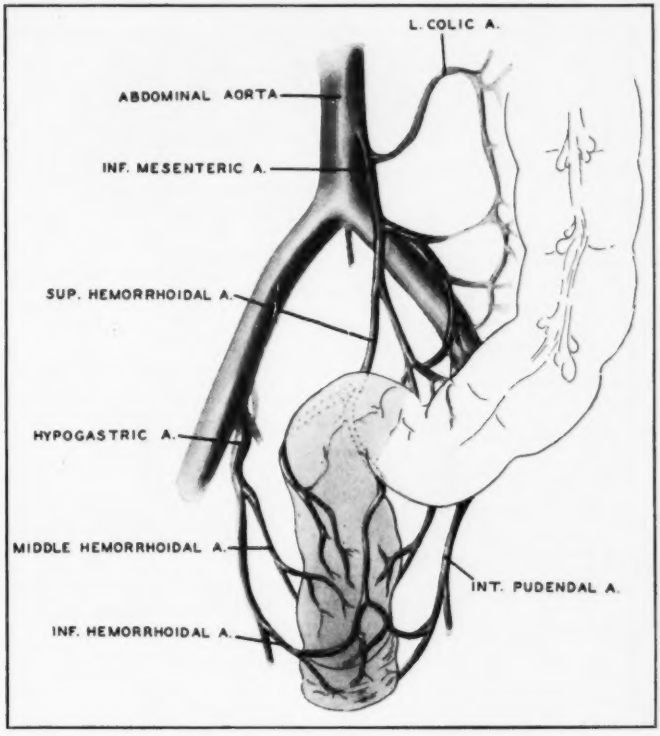

Fig. 2.—Blood supply of the rectosigmoid.

growth. After a careful analysis of the literature, the authors made this statement:

> In more than 239 of the 507 cases from the literature in which the removed tissues were completely examined, nodal metastasis was observed to occur. Of these only 8 gave evidence of an involved node below the level of the lesion itself . . . in 7 of the 8 cases there was no spread below the 2 centimeter level,

which when interpreted in the terms outlined in this study remains insignificant. . . . When such retrograde spread can be demonstrated, it is an indication that upward normal channels have been blocked.

It cannot be emphasized too strongly that metastasis via the lymphatics is primarily, if not invariably, upward. The more malignant and extensive the growth, the greater is the chance of nodular involvement. The venous channels should be accorded a high rating in responsibility for secondary lesions, as they furnish avenues for transmission

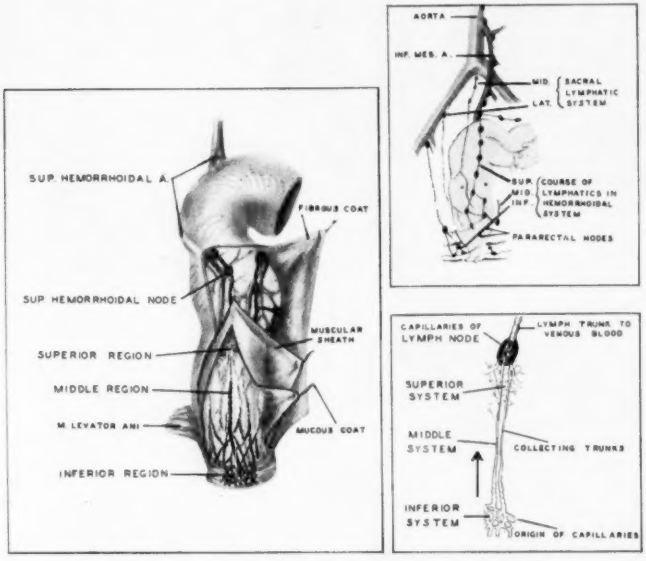

Fig. 3.—Lymphatics of the rectosigmoid.

of the disease; it is not uncommon for one to find extensive hepatic involvement without the lymph nodes having been invaded. It should not pass unnoticed that early recurrence or inoperability is often predicated on an extension to a contiguous structure, and lymphatic involvement may play a minor part in the prognosis. This leads to the conviction, substantiated by the examination of 1,339 nodes by Glover and Waugh, that any growth of the rectosigmoid region resected 2 cm. or more below its lowest palpable margin has a less than 1 per cent chance of metastasis through nodes below this level; it is not necessary

for the anus to be sacrificed if the growth is 6 cm. or more above the pectinate line. Therefore, it would appear that if a resection can be done 2 cm. or more below the growth in this region the sphincter can remain unimpaired and an anastomosis made by one of two methods,

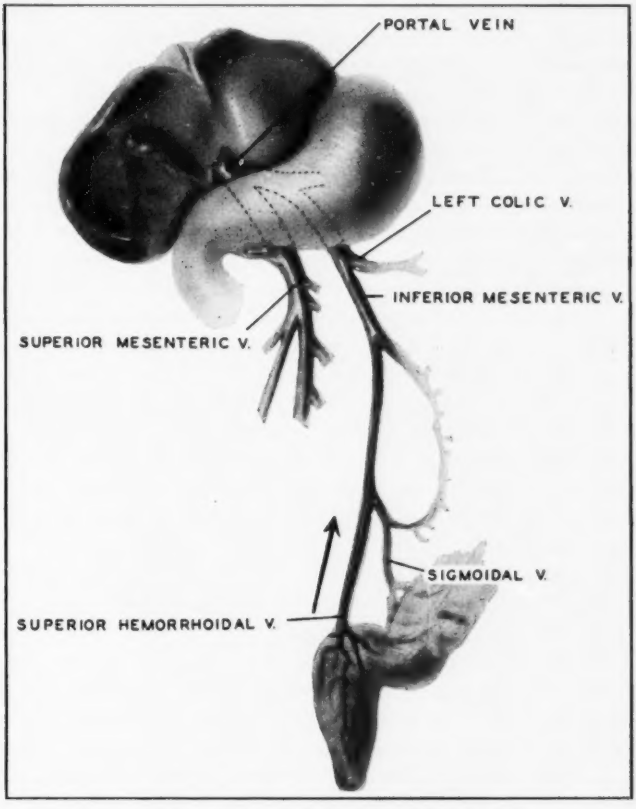

Fig. 4.—Course of hepatic metastasis.

the intra-abdominal method or a combined abdominal and perineal method.

One cannot find fault with the mortality of the combined abdomino-perineal operation in the hands of such excellent operators as Jones or Lahey, but the permanent colostomy opening plagues the operator and

the patient. It is doubtless true that many patients learn to take such excellent care of a colostomy opening that they are never suspected of having an artificial anus, and they pursue gainful occupations. Nevertheless, a colostomy opening is a physical handicap and a mental hazard. I have yet to see the first patient who would not exchange a good colostomy opening for a functioning anus, were it possible for him to make such a transfer. There can be no question that the possibility of a permanent colostomy opening deters many from an operation which could well result in a cure; on the other hand, I never knew of a patient who committed suicide because he was the unproud possessor of a colostomy opening.

Babcock and Bacon have been the chief proponents of the operation to preserve the sphincter, and they are entitled to much credit for their persistent efforts and pioneer work. When this operation has been performed by others, the results have been somewhat disappointing, but the fault may have been with the operator and not the operation. It is impossible for one to predict prior to operation just what sort of sphincter control will follow. Some patients complain of strictures; others of incontinence, with thin stools. All in all, the aforementioned operation seems to fall just short of an ideal procedure. During the past few months I have undertaken to modify the combined abdominal and perineal operation in such a manner that perfect sphincter control is assured. I claim no originality for the operation, as it is merely a revival of a discarded one, discarded because it was cursed with complicating infections.

The introduction of antibiotics in recent years has removed many of the dangers attending intestinal surgery, so that surgeons may, without fear of peritonitis, do an open anastomosis and take other liberties with the gastrointestinal tract never before dreamed of. By the intelligent use of the sulfonamide compounds, penicillin and streptomycin, alone or in selected combinations, and through evacuation and decompression, it is possible for the surgeon to minimize the danger of infections in most intestinal operations. The elimination of infections by these means makes possible the preservation of the anal sphincter in the operation described.

The operation proceeds as in the routine abdominoperineal resection, with a low midline incision from the pubes to the umbilicus, or higher, with the patient in the Trendelenburg position. Exploration for metastasis and estimation of the extent of the growth should be the next steps. The sigmoid is isolated by dividing its peritoneal attach-

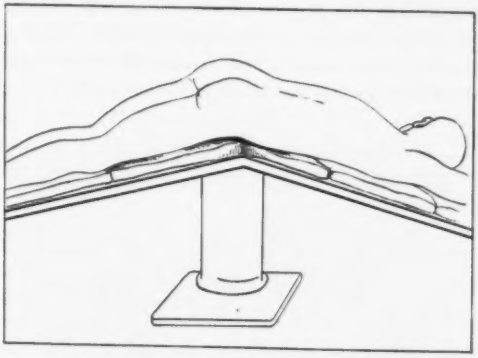

Fig. 5.—Position of the patient at the second stage of the operation.

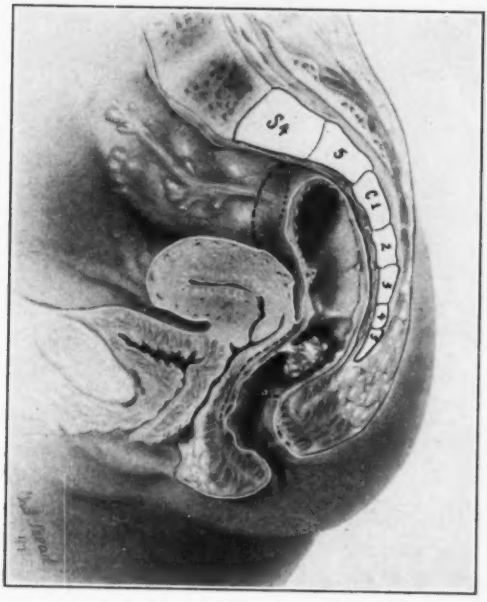

Fig. 6.—Lateral view, carcinoma in situ.

ments laterally and from the bladder, ligating the superior hemorrhoidal vessels and detaching the bowel well down into the pelvis, to the tip of the coccyx. The growth can be palpated and evidence of nodular involvement noted, if present. After the bowel is thoroughly freed, a silk thread may be placed as a marker proximal to the growth, through

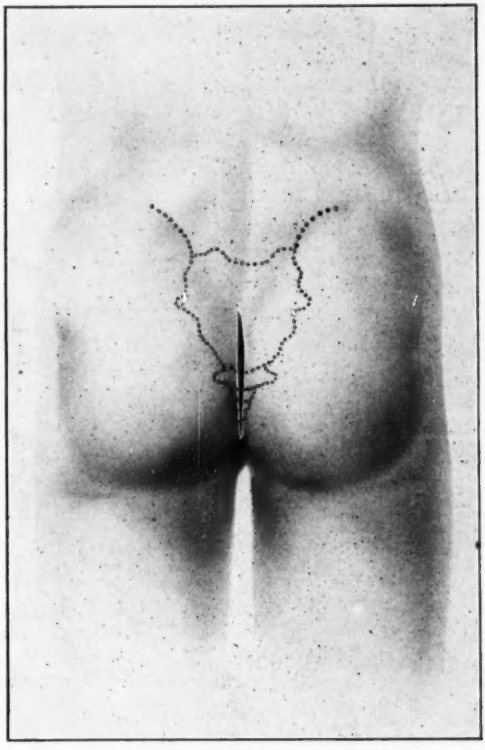

Fig. 7.—Second incision.

the outer coats of the bowel at the lowest point where the circulation in the colon is adequate. The highest level of the sigmoid that can be brought down to the anus depends on the anatomic situation and possibly on the surgeon; Bacon claimed to have brought the transverse colon down in the "pull-through" operation. It is mandatory that the upper end of the resected segment be not lower than its adequate

blood supply. When the segment of the bowel to be resected is completely liberated, all attachments should be divided to permit the segment to be displaced in the pelvis, with sufficient freedom to allow the site of the proposed division of the bowel to be placed in the pelvis without tension. A new floor of the pelvis is constructed from the peritoneum, which has been separated laterally and anteriorly, and closed snugly above the rectosigmoid deep in the pelvis. The abdominal wound is then closed and the patient placed face downward on the

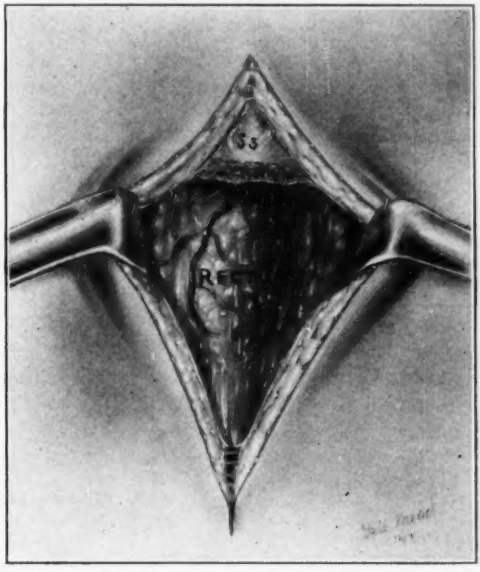

Fig. 8.—Second incision retracted.

table in a jackknife position. The buttocks can be kept apart by adhesive straps for a better approach to the operative field. An incision is made from the middle of the sacrum to 3 cm. above the anus. The wound is deepened and retracted. The coccyx, the fifth and part or all of the fourth sacral segment are removed. The sacral arteries lie near the middle line, close to the pelvic side of the sacrum. They should be ligated and divided. As the separation of the tissues in the midline is continued, the pelvis below the new peritoneal floor is invaded, and the loose rectosigmoid segment can be drawn through

the incision. The marker of silk suture can be identified, and a Stone clamp placed at, or above, this level. About 3 to 4 cm. above the anus a second Stone clamp is applied and the section removed between the two clamps, which are then disengaged. The open ends of the bowel are approximated and held by a guy suture on either side to facilitate the open anastomosis. I use fine chromic surgical gut U. S. P. on atraumatic® needles. The first row is one of the Lembert type and approxi-

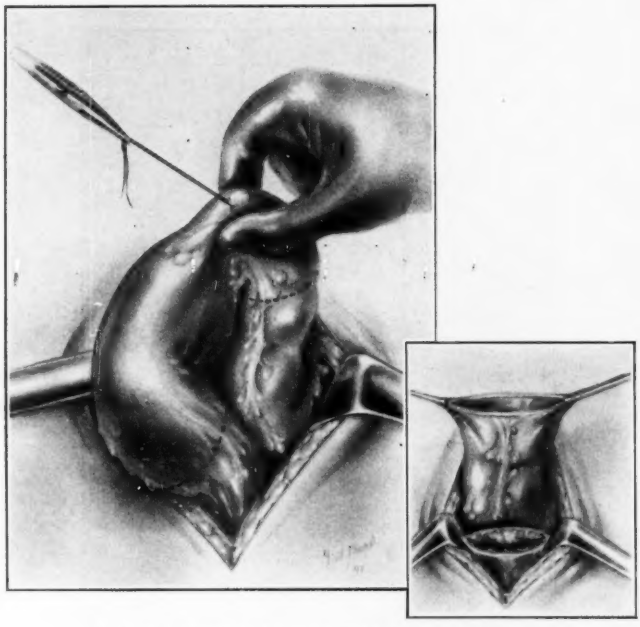

Fig. 9.—Tumor and rectosigmoid segment delivered.

mates the posterior surfaces (anatomically the anterior surfaces); this is followed by a locking stitch through all layers. These two rows of sutures firmly bind the two posterior walls. The binding of the anterior wall is completed by a Connell stitch, over which the last, or Lembert, row completes the anastomosis. The guy sutures are removed, and the bowel is dropped back into the pelvic cavity. A cigaret drain is placed in the lower end of the wound. The use of a rectal tube passed through the anastomosis is optional, as it may prevent edema at the point of

anastomosis. It can be introduced before completion of the anastomosis, to avoid any possible trauma and to insure its proper position in reference to the anastomosis.

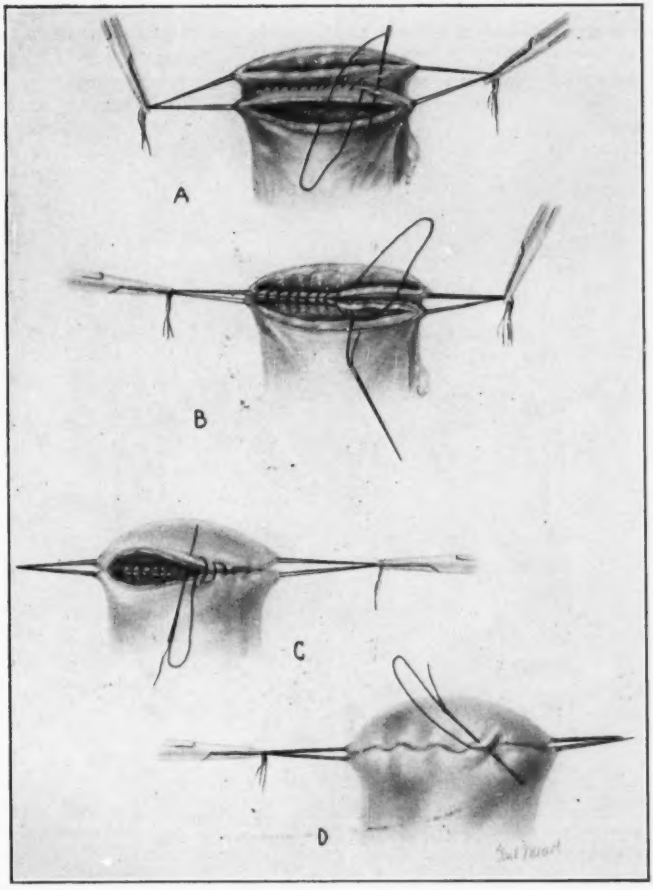

Fig. 10.—Anastomosis, by steps.

The convalescence is a matter of two weeks or less, with excellent sphincter control. My experience with the operation is confined to 10 cases, a number insufficient to permit one to make convincing deduc-

tions, but warranting further exploration in this field. The low end to end intra-abdominal anastomosis in the surgery of the rectosigmoid region, as described and practiced by Dixon, appears to have a wider field of application than that in which it is employed at present. However, so few operators possess the technic and dexterity of Dixon that the operation has not been popularized, notwithstanding its sound

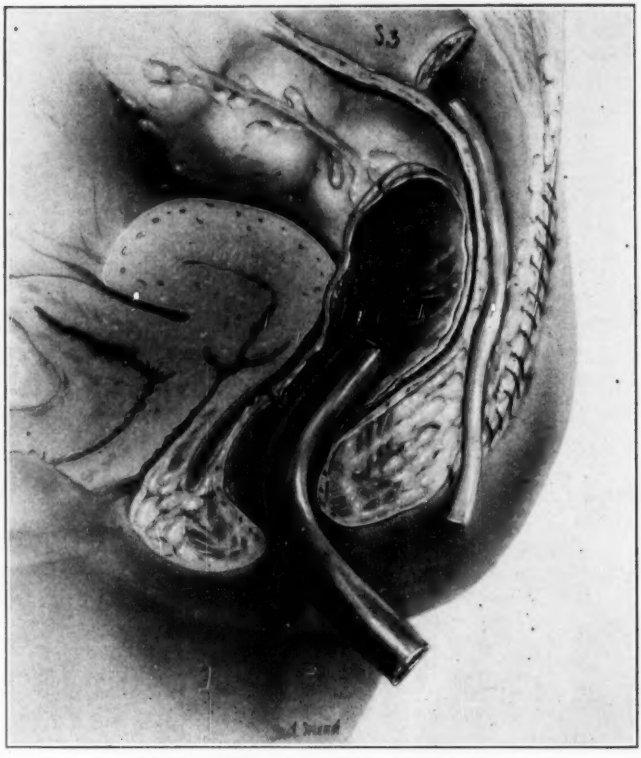

Fig. 11.—Operation completed, lateral view.

principles. To some extent the operation here described is a substitute, particularly in those cases in which the malignant growth is 6 to 15 cm. above the anal sphincter. The operation is illustrated by 4 cases.

REPORT OF CASES

Case 1.—M. N., a married white woman, aged 46, a clerk, was admitted to the hospital on Feb. 9, 1947. The chief complaint was bleeding from the rectum.

The patient's mother had died at 75 and her father at 77, both of "bad heart." There was no history of malignant disease in the family. The past medical history revealed the usual childhood diseases without complications. "Thyroid trouble" had been experienced for nine years prior to subtotal thyroidectomy in May 1946; the diagnosis had been Hashimoto's disease (struma lymphomatosa). A hemorrhoidectomy had been done in 1938. In 1922 a bilateral salpingectomy and an appendectomy had been performed. Prior to her present illness the patient had been under observation for two months for a small cystic mass in each breast.

The present illness began eight weeks prior to her admission with the appearance of constipation (for the first time in many years), and the condition had failed to respond to laxatives. Five weeks before her admission dark red blood had been noted in the stools, and this had been present intermittently since. Three weeks prior to admission the patient had begun to have severe, cramping abdominal pain. Some anorexia had been present for the past month. There had been a bowel movement every three or four days during the present illness. Review of the systems showed an essentially normal condition except for moderate dyspnea on exertion.

On examination the patient appeared nervous but fairly well nourished. She was not confined to bed. The normal weight had been 105 pounds (47.6 Kg.), and the present weight was 115 pounds (52.1 Kg.). The pulse rate was 80 per minute; the blood pressure, 120 systolic and 80 diastolic. The head and neck were normal except for a well healed collar incision. The upper outer quadrant of each breast presented a firm, freely movable nodular area, 1 cm. in diameter and nontender. There were no palpable lymph nodes. The heart and lungs were normal. The abdomen was slightly distended. Peristalsis was hyperactive. There were no palpable masses or areas of tenderness. The liver, kidneys and spleen were not palpable. Rectal examination revealed well healed hemorrhoidectomy scars. The sphincteric tone was active and normal. Sigmoidoscopic examination, done prior to admission, revealed a fungating mass on the posterior wall, 10 cm. from the anus; this mass did not involve the circumference of the bowel. Biopsy diagnosis of this mass was reported as adenocarcinoma grade 2.

After routine preparation, a combined abdominosacral resection of the rectosigmoid was done, with primary open, end to end anastomosis just above the internal sphincter. Examination by palpation revealed no evidence of metastasis to the regional lymph nodes or the liver.

Pathologic examination of tissues was reported on as follows: "The specimen submitted for examination consisted of a piece of large bowel measuring 8 cm. in length and 3.5 cm. in diameter. The mucous membrane was seen to be interrupted in various places by small plaques, which were of increased firmness and averaged 4 mm. in diameter. Midway in this piece of bowel was a plaque, measuring 1 cm. in diameter, which was slightly raised and apparently somewhat polypoid. Sections through this nodule revealed it to consist of irregular, anaplastic glands lined with embryonic columnar epithelial cells. The glandular pattern was fairly regular, although the lumens varied greatly in size. The nuclei were hyperchromatic, and mitotic figures were seen in various phases of development. Invasion, however, did not appear to be very deep in the muscular wall. The diagnosis was adenocarcinoma."

The postoperative course was uneventful. The temperature rose to 99.6 F. on the first day and fluctuated between this and normal for five days, returning

to normal. The Levin tube was removed after forty-eight hours, and the patient was given clear liquids freely. The rectal tube was removed on the fifth day. The abdominal sutures and the posterior drains were removed on the sixth day. There was no drainage. Gas was passed freely. There was a normal bowel movement on the tenth day, and the patient was discharged on the twelfth day, with perfect sphincter control. Since the patient's discharge from the hospital her course has been marked by constipation, due to a large neurotic element. On Aug. 15, 1947, digital rectal examination indicated an adequate lumen. Sigmoidoscopic examination revealed complete healing, and the sphincter control has been perfect.

CASE 2.—M. H., a white housewife, aged 35, was admitted to the hospital on Jan. 16, 1947. The chief complaint was vaginal and rectal bleeding. The family history was without significance. The past medical history was essentially noncontributory except for pyelitis for eighteen months, complicated by meningitis (causative organism unknown to me). There was no history of serious illness, accident or operation. The patient had borne three children and was pregnant for the fourth time.

The history of the present illness indicated that in August 1946 the patient had noted bleeding from the rectum. There had been a constant loss of blood in slight amount with occasional spurts of blood. The patient had consulted a physician and had been informed that she had a growth in the rectum. She, however, had determined to have another child before having surgical treatment. The last menstrual period had been in October 1946, and pregnancy was of two and one-half months' duration. After a sigmoidoscopic examination and biopsy of the mass in the rectum, the patient had been advised to have a therapeutic abortion. The specimen taken for biopsy was reported on Jan. 9, 1947 to be of an adenocarcinoma arising in a polyp. On the day prior to admission the patient had begun to have mild vaginal bleeding, and incomplete abortion occurred on the following day. She was taken to the operating room and dilation and curettage was done, with removal of the retained secundines. At this time 2 gold radon seeds, 2 millicurie units each, were inserted into the mass on the posterior rectal wall, 7 cm. from the anus. The patient was discharged from the hospital on January 20, as improved, to be readmitted after a convalescent period of one month.

She was again admitted on February 24, after an uneventful recovery. There had been no loss of weight or gastrointestinal symptoms except for the continuance of slight rectal bleeding. Review of the systems revealed a history of persistent mild headache, relieved by acetylsalicylic acid U.S.P. The patient had hay fever, for which she continually used ephedrine nose drops.

Examination revealed that the patient was well developed and well nourished; the pulse rate was 70 per minute and the blood pressure 128 systolic and 80 diastolic. The head, neck, heart, lungs and extremities were essentially normal. The abdomen was flat, and there was no tenderness, rigidity or palpable mass. The abdominal organs were not abnormal to palpation. Rectal examination revealed normal sphincteric tone. A hard mass could be palpated on the posterior rectal wall. Sigmoidoscopic examination revealed a polypoid, ulcerated mass with elevated edges, bleeding easily, on the posterior rectal wall at a depth of 7 cm.

After intensive preparation over a period of five days, a combined abdominosacral resection of the rectosigmoid colon was performed. There was no palpable evidence of metastasis to the liver or the regional lymph nodes. Results of pathologic examination were reported: "Section of the colon disclosed a small cauli-

flower shaped, ulcerated mass, approximately 4 cm. in diameter. The ulceration extended down to the serosa but did not perforate it. Sections revealed numerous irregular glands composed of embryonic epithelial cells, which appeared to be invading in various directions. Their nuclei were hyperchromatic, and mitotic figures were observed. There were an associated moderate fibrosis and dense round cell infiltration. The diagnosis was adenocarcinoma."

The postoperative course was smooth. The gastric suction was discontinued after seventy-two hours. The posterior dressings were changed as necessary because of a moderate amount of serosanguineous drainage. The patient was given clear liquids freely. The rectal tube was removed on the fifth day. On the sixth day the abdominal sutures and posterior drains were removed. The abdominal incision healed by first intention. On the seventh day the posterior sutures were removed. A small sinus with serous drainage persisted for fourteen days, with complete healing. There was a spontaneous bowel movement on the seventh day. The patient was discharged on the sixteenth day, well healed and having bowel movements without aid. Sphincter control was perfect. Since the patient's discharge bowel control has been perfect. The hemoglobin has risen from 65 to 82 per cent. Rectal examination revealed a completely healed, moderately contracted but adequate site of anastomosis through which a proctoscope was passed freely. Examination on Aug. 29, 1947 confirmed this statement.

Case 3.—B. F., a white woman, aged 55, a housewife, was admitted to the hospital on March 25, 1947. The chief complaint was bleeding from the rectum. The family history was noncontributory. There was no history of malignant disease. The past medical history revealed the usual childhood diseases with no complications. The patient complained of mild arthritis. There had been no serious illness or operation. The menopause had occurred at the age of 50 and had been uneventful. There had been no pregnancies.

The onset of the present illness had been nine months prior to admission, when the patient had noted blood mixed in the stool and at times bright blood prior to a passage. At times the blood had been bright and at times dark. At first the patient had been constipated, but the bowels moved daily at the time of her admission to the hospital. The appetite had been fair, but she complained of some gas and belching. There had been no abdominal pain. Advice had been sought from a physician in another city, who had told her that she had a tumor of the rectum. A specimen for biopsy was taken and reported to be of adenocarcinoma high grade 2. Her weight had been stable at 128 pounds (58.1 Kg.). Review of the systems disclosed an essentially normal condition except for the present illness.

On examination the patient was ambulatory and in a fair state of nutrition, weighing 128 pounds (58.1 Kg.). The pulse rate was 76 per minute, and the blood pressure 140 systolic and 80 diastolic. The head, neck, lungs and heart were not abnormal. The abdomen was flat and free of scars. There was slight infraumbilical tenderness. There were no palpable masses, and the abdominal organs were not enlarged or tender. Sigmoidoscopic examination revealed a polypoid, ulcerated mass on the right posterolateral wall of the rectum, at 12 cm. This mass did not extend around the circumference of the bowel. Anoscopic examination revealed small internal and external hemorrhoids.

After routine preparation of the bowel, a combined abdominosacral resection of the rectosigmoid was done. Primary end to end anastomosis was done 3 cm.

above the internal sphincter. There were no evident metastases to the liver or the regional lymph nodes. The pathologic report was as follows: "Sections through the colon revealed the presence of a malignant process arising in the crypts of Lieberkühn and invading in all directions in a most irregular and haphazard fashion. This invasion included the submucosa and the musculature. The growth maintained an acinous pattern, and the cells were rather embryonic in character, showing the presence of innumerable mitotic figures in all stages of development and having hyperchromatic nuclei. In the deeper structures there were numerous pockets and nests of neoplastic cells. The picture was that of an adenocarcinoma of the cylindric cell type of a relatively high grade of malignancy."

The postoperative course was uneventful. The Levin tube was removed after forty-eight hours. Flatus was expelled through the rectal tube after seventy-two hours. The rectal tube was removed on the fifth day. On the sixth day a stool was obtained with castor oil. Abdominal sutures were removed on the sixth day, and the incision was healing well. On the seventh day the posterior drains were removed, and the sutures, on the tenth day. The incisions were healing well, and the bowels were functioning adequately with perfect sphincter control on the patient's discharge, on the fourteenth day.

One week after discharge, the patient was seen again. At this time there was a small amount of purulent discharge from the upper end of the posterior incision. The anastomosis was patent and roomy and completely healed. The bowels moved freely, and the sphincter control was perfect. Drainage had stopped, and healing was complete in two weeks. Examination two months later showed that the incisions were well healed, the patient had gained weight and the bowels moved daily. Examination on August 30 showed an adequate lumen and perfect sphincter control.

Case 4.—H. L., a white man, aged 57, unemployed, was admitted to the hospital on June 14, 1947. The family history was noncontributory, and there was no history of malignant disease. The patient's medical history revealed that in 1924 he had had pulmonary tuberculosis, which had been arrested after one month of bed rest. The disease had become active again in 1937, at which time the patient had been institutionalized for several months. After this treatment he had been under a regimen of complete or partial bed rest for seven years. Again, he had been classified as having an arrested case. In 1915 he had had gonorrhea with stricture of the urethra, responding to dilations only. There had been no operation or serious injury.

The onset of the present illness had been two months prior to admission with constipation, followed by blood-streaked stools for two days. The bleeding had returned one month before and had continued up to admission. There had been no further constipation and no diarrhea. The blood had always appeared bright red. The stools had been of normal size and character. There had been rectal tenesmus for the past month. There had been no loss of weight or digestive disturbance of any kind. The review of the systems showed an essentially normal condition except for the present illness.

On examination the patient appeared well developed and well nourished, with a weight of 157 pounds (71.2 Kg.). The pulse rate was 68 per minute and the blood pressure 130 systolic and 80 diastolic. The head and neck were essentially normal. The chest was clear. The heart was not abnormal. The abdomen showed

no scars, distention, tenderness or rigidity. There were no palpable masses. The abdominal organs were not palpably abnormal. Sigmoidoscopic examination prior to admission revealed a small, villous lesion, raised and bleeding easily, on the right anterior wall at a depth of 13 cm. Biopsy diagnosis was reported as adenocarcinoma grade 1.

Five days prior to admission, the patient was placed under routine preparation for resection of the bowel. Abdominosacral resection was done, with removal of the tumor-bearing area, 10 cm. above and 10 cm. below the lesion. Primary open end to end anastomosis was done 7 cm. above the internal sphincter. There were no evident metastases to the liver or the regional lymph glands. The pathologic report was as follows: "Sections through the colon showed the presence of an extensive malignant process arising from the crypts of Lieberkühn. The pattern in general was glandular. The cells were young. They showed many hyperchromatic nuclei and numerous mitotic figures in various stages of development. There were some ischemic necrosis in the surrounding stroma and a considerable degree of round and plasma cell infiltration. Throughout all coats there were small pockets and nests of neoplastic cells. The diagnosis was adenocarcinoma of the colon grade 3."

The postoperative course was marked by moderate abdominal distention, in spite of Wangensteen suction, and the patient's inability to urinate spontaneously for six days. Gas was passed through the rectal tube on the second day. The Levin tube was removed after seventy-two hours. The colon tube was removed on the fifth day. The abdominal sutures were removed on the sixth day, and the incision was healing well. On the seventh day the posterior drains were removed, and the patient was allowed out of bed. There was a small amount of purulent drainage from the upper end of the posterior incision, and this cleared completely in ten days. On the eleventh day the patient was discharged, with the incision healing well, and with satisfactory bowel movements.

The patient returned to the office at the end of ten days. He was completely healed; bowel movements were satisfactory, and the sphincters were under perfect control. Examination on August 15 showed an adequate lumen with complete healing of the anastomosis.

SUMMARY

In cases of malignant growths in the rectosigmoid region, and possibly higher, the anal sphincter may be preserved by a combined abdominoperineal resection, completing the anastomosis through a posterior incision by removing the coccyx and the lower two segments of the sacrum. An open anastomosis is safe if the preoperative preparation takes advantage of the antibiotics now available. Recurrence from metastasis through lymph nodes about the anal stump should be minimal. In less than 1 per cent of cases analyzed has it been shown that lymphatic involvement is present more than 2 cm. below the growth, and then only when higher lymphatics are already invaded. The risk is not increased; sphincter control is complete, and the convalescence is a matter of less than two weeks. The operation requires no greater skill than is employed in routine resections. No originality is claimed for this procedure, as it has been tried and abandoned in the past,

but the inhibition of infection by the antibiotics justifies the revival of the operation. Whether the rate of five year cures will equal that of the abdominoperineal operation with a colostomy is purely speculative at present; but, awaiting statistical data, I believe the operation as I have described it justifies further trial. This operation may prove useful in those cases of ulcerative colitis in which an almost complete colectomy is required. If the terminal few centimeters of the rectum is not involved, an anastomosis with the ileum by the posterior approach may prove practical so that an ileostomy is avoided. I have not had an opportunity to apply this suggestion in actual practice.

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BLEEDING CONTROL AND ABSORPTION OF SYNTHETIC ADHESIVES

A Second Report

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IN A PREVIOUS publication[1] the practicability of controlling bleeding in abdominal viscera by the application of synthetic adhesives was demonstrated in rabbits and mice.

Analogues of the commercial so-called Scotch tape were used in enclosing gaps in the liver from which sections had been extirpated. The animals were later killed and the tissue reactions studied. Criteria considered essential for a satisfactory synthetic adhesive were (1) tack, or ability to adhere to viscera or tissue sufficiently to control bleeding; (2) absorbability, with the minimum of surrounding tissue reaction, and (3) sterilization potential.

With the cooperation of the Minnesota Mining and Manufacturing Company, makers of Scotch tape, special synthetic adhesive films have been developed in the attempt to embody these requisites in one tape structure.

As this investigation, begun in September 1943, is concerned with the hemostatic and absorptive qualities of certain particular synthetic adhesives in rats, mice, rabbits, dogs and cats, no attempt has been made at this time for a concurrent comparison with fibrin foam[2] and gelatin sponge.[3]

Aided by a grant from the Minnesota Mining and Manufacturing Company, St. Paul, Minn.

From the Department of Experimental Medicine, University of Southern California Medical School.

Presented before the Society of Experimental Biology and Medicine, Southern California Chapter, Feb. 23, 1949.

1. Lowry, M. L.: Synthetic Adhesives in the Treatment of Wounds of the Liver and Other Surgical Conditions, Arch. Surg. **52**:160-171 (Feb.) 1946.

2. Bailey, O. T., and Ingraham, F. D.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XXI. The Use of Fibrin Foam as a Hemostatic Agent in Neurosurgery; Clinical and Pathological Studies, J. Clin. Investigation **23**:591-596, 1944. Bering, E. A., Jr.: Chemical, Clinical and Immunological Studies on the Products of Human Fractionation: XX. The Development of Fibrin Foam as a Hemostatic Agent and for Use in Conjunction with Human Thrombin, J. Clin. Investigation **23**:586-590, 1944.

(Footnotes continued on next page)

EXPERIMENTAL WORK

These studies are divided into two categories, differing in scope. Section 1 supplements the original preliminary report in search for a nonirritant, absorbable adhesive capable of controlling hemorrhage within the body. Section 2 is concerned with tissue reaction and absorption qualities of the component parts of one specially prepared synthetic adhesive tape.

SECTION ONE

Rabbits and dogs were used in these experiments. While no effort was made to sterilize the plastic films, an attempt at surgical asepsis was carried on. An operative procedure similar to the original technic was utilized, consisting of the excision in the anesthetized animal of a pie-shaped section of liver ¾ to 1 inch (1.9 to 2.5 cm.) in diameter and the enveloping of the resulting hiatus above, below and at the edge with special adhesive films. No other means of hemostasis was used, and the cut edges of the liver were not brought into apposition. The abdomen was closed with linen sutures and the animal permitted to recover from the ether or pentobarbital sodium anesthetic. Two to seven weeks later the animals were killed and microscopic sections made of the hepatic tissue reaction and the extent of absorption of tape.

Experiments on Rabbits.—White male rabbits 4 to 10 months old were used. The anesthetic was ether. Various, specially constructed synthetic plastic films, coated with different synthetic adhesives and forming a clear, transparent tape, were applied at operation.

Abdominal adhesions, while few, were most pronounced in rabbits 1, 4 and 5. In microscopic examinations, sections of liver from rabbits 7, 9 and 10 displayed a minimum scar tissue formation, fading within a short distance to apparently healthy hepatic parenchyma.

Experiments on Dogs.—Similar extirpation of sections of liver and enclosure of the wound in a Scotch tape analogue were performed on 7 dogs, all of which made uneventful recovery. Pentobarbital sodium was used intravenously for anesthesia and linen thread for abdominal closure. Autopsy, with microscopic study of the liver, was accomplished on all animals except dog 1, which ran away from his kennel on the fourth week. A specially prepared tape eliminating the rope stock binder, consisting of the polyvinyl alcohol film faced with synthetic resin, was the adhesive tape used in all these animals.

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3. Jenkins, H. P., and Janda, R.: Studies on the Use of Gelatin Sponge or Foam As an Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins, Ann. Surg. **124**:952-961, 1946. Jenkins, H. P.; Sena, E. H.; Owen, H. W., and Jampolis, R. W.: Present Status of Gelatin Sponge for the Control of Hemorrhage, J. A. M. A. **132**:614-619, 1946.

In none of the animals was any gross hepatic damage evidenced; microscopic examination revealed normal hepatic parenchyma a short distance from the extirpation wound. The hepatic reaction was a mild scar, not an abscess, and intra-abdominal adhesions were at a minimum, except in dog 3, which had a draining sinus.

TABLE 1.—*Experiments on Rabbits*

Rabbit	Tape	Results
1	Polyvinyl alcohol, Buna S	Uneventful recovery; killed 14 days postoperatively; intrahepatic cyst; mild fibrous capsule; particles of undissolved tape
2	Polyvinyl alcohol, Buna S	Died 6 hours postoperatively, from liver hemorrhage
3	Polyvinyl alcohol, Buna S	Uneventful recovery; killed seventh postoperative day; intrahepatic cyst; mild fibrous capsule; undissolved tape
4	Polyvinyl alcohol, rope stock filler, synthetic resin	Uneventful recovery; killed at 14 days; intrahepatic abscess; heavy fibrous capsule reaction; undissolved tape
5	Polyvinyl alcohol, rope stock, synthetic resin	Died on third day of diffuse peritonitis
6	Polyvinyl alcohol, synthetic resin (without rope stock filler)	Uneventful recovery; killed at 7 days; small intrahepatic cyst; mild fibrous reaction; undissolved tape
7	Polyvinyl alcohol, synthetic resin (without rope stock filler)	Uneventful recovery; killed at 14 days; small intrahepatic cyst; mild fibrous capsule; undissolved tape
8	Polyvinyl alcohol, synthetic resin	Uneventful recovery; killed at 14 days; intrahepatic cyst; mild fibrous capsule; undissolved tape
9	Polyvinyl alcohol, synthetic resin	Uneventful recovery; killed at 21 days; small intrahepatic capsule with particles of undissolved tape
10	Polyvinyl alcohol, synthetic resin	Uneventful recovery; killed at 28 days; small intrahepatic capsule; mild fibrous tissue reaction; particles of undissolved tape

TABLE 2.—*Experiments on Dogs*

Dog	Results
1	Ran away at four weeks, before reoperation; apparent complete recovery
2	Killed four weeks postoperatively; small hepatic scar, within which were particles of undissolved tape; no intra-abdominal tape discovered
3	Killed at three weeks; small hepatic scar; draining sinus from omentum in region of operative wound; while no tape was found, it is a possible cause of the draining sinus, although a previous gastroenterostomy should be considered
4	Killed at five weeks; small intrahepatic cyst; tape found absorbed in abdomen, with practically no surrounding reaction
5	Killed at six weeks; small intrahepatic scar; tape not found within liver or abdomen
6	Killed at seven weeks; mild hepatic scar; tape not discovered in liver or abdomen

In Vitro Absorption.—Small squares of tape of (1) cellophane, rope stock, crude rubber; (2) acetate fiber, rope stock, polyisobutylene; (3) polyvinyl alcohol, rope stock, synthetic resin; (4) polyvinyl alcohol, Buna S (without rope stock), and (5) polyvinyl alcohol, synthetic resin (without rope stock) were immersed in (*a*) tubes of gastric juice aspirated from a healthy male (free hydrochloric acid, 35 degrees; total acidity, 50 degrees) and (*b*) tubes of normal blood serum.

At the end of four weeks none of the synthetic tape structures was dissolved in the gastric juice nor in the human blood serum.

SECTION TWO

As a result of the first phase of these investigations, the tape found to incorporate the most promising properties of (1) bleeding control and (2) absorbability, with minimum tissue reaction, was the synthetic resin adhesive coated directly on a polyvinyl alcohol film. An intensive study of these two complex chemical substances, both individually and as a combined adhesive tape unit, was undertaken in rabbits, rats, mice and a cat.

To insure an absorption study of the material definitely within the liver and the spleen, the technic of placing the film over a pie-shaped excision was abandoned. Instead, these vascular organs were incised transversely, in the manner of a sandwich slice. The material to be studied was placed deep in the crevice between the two layers, which were then approximated without the use of a needle suture. The upper and lower portions were held together in most cases by sticking the synthetic resin–polyvinyl alcohol tape around the wound. In a number of instances a special liquid synthetic adhesive, similar in chemical composition to the inserted material, was introduced within the liver or spleen to keep the layers in apposition. It was always possible to control the viscus bleeding sufficiently to allow adherence of the plastic tape; digital pressure with gauze aided in temporarily drying the bleeding bed sufficiently to permit sticking of the adhesive film. An annoying technical problem is the tendency of the sticky film to adhere to gauze and scissors, a difficulty which can be overcome by wetting the cutting instrument.

Another method for implantation of the synthetic resin, the polyvinyl alcohol film and the combined plastic film was the slitpocket wedge incision on the surface of the liver or spleen, with the material held in place by an envelope of adhesive film over the viscus groove. In a few spleens the film was drawn completely through a sagittal incision.

Ether was the anesthetic, and linen thread was used for the closure of the abdomen. The animals, returned to their cages and given a normal diet, were killed at intervals of from one week to eight months later, the abdominal cavity observed for tissue reaction and microscopic sections of the liver and spleen examined for absorption data on the implanted materials.

Three synthetic materials were studied in 235 animals. When the synthetic resins were used (table 3), the weights of the implanted globules of this rubbery mass varied from 25 to 350 mg. The portions of transparent polyvinyl alcohol film (table 4), when inserted, weighed from 7 to 80 mg., with the squares ranging from 2 to 6 cm. in width.

Similar but slightly heavier particles were implanted in the complete tape study (synthetic resin adhesive on a polyvinyl alcohol film, table 5).

Experiments on intraperitoneal absorption were accomplished by implanting particles of similar materials within the abdominal cavity,

TABLE 3.—*Synthetic Resin Implant*

A. Liver

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	3	1	2	4	1	..	..	12
Not found	..	..	1	1	1	..	..	..	3

B. Spleen

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	1	1	1	..	..	..	..	4
Not found	..	..	..	1	1	..	..	..	2

C. Intrascapular

	Months								
	1	2	3	4	5	6	7	8	Total
Found	3	3	5	11	3	..	..	..	25
Not found	..	1	1	2	1	..	..	..	5

D. Intra-Abdominal

	Months								
	1	2	3	4	5	6	7	8	Total
Found	2	2	3	9	6	2	..	..	24
Not found	..	1	2	1	2	1	1	..	8

TABLE 4.—*Polyvinyl Alcohol Film Implant*

A. Liver

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	2	1	1	3	1	..	..	9
Not found	..	1	1	2	2	..	1	..	7

B. Spleen

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	1	..	..	1	1	1	..	5
Not found	..	..	..	1	1	..	..	..	2

C. Intrascapular

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	2	1	2	8	4	..	..	19
Not found	..	1	..	1	1	1	..	..	4

D. Intra-Abdominal

	Months								
	1	2	3	4	5	6	7	8	Total
Found	2	1	..	4	4	3	1	..	15
Not found	..	..	1	3	4	8	4	..	20

closing the incision with linen sutures and subjecting the animals to autopsy later at various intervals.

Subcutaneous absorption was studied by a technic devised by Lattes and Frantz,[4] in which the material is inserted into a tunnel under the skin of the back through a small transverse intrascapular incision.

For convenience in tabulation, the rabbit, mice and rat experiments are grouped under one heading. Both the rabbit and the mouse were early discarded as experimental animals, the former because of susceptibility to infection and the latter on account of technical operative difficulties with the tiny livers and spleens. Surgical asepsis is not

TABLE 5.—*Polyvinyl Alcohol–Synthetic Resin Tape Implant*

A. Liver

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	1	1	2	2	..	1	..	8
Not found	..	..	..	..	3	2	..	1	6

B. Spleen

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	1	1	1	..	..	..	1	5
Not found	..	1	..	1	1	..	..	..	3

C. Intrascapular

	Months								
	1	2	3	4	5	6	7	8	Total
Found	1	1	1	1	1	..	..	..	5
Not found	..	..	1	..	1	..	..	..	2

D. Intra-Abdominal

	Months								
	1	2	3	4	5	6	7	8	Total
Found	7	3	3	4	5	5	1	..	28
Not found	..	3	3	2	3	2	..	1	14

TABLE 6.—*Percentage of Autopsies in Which Material Was Not Found*

	Synthetic Resin	Polyvinyl Alcohol Film	Polyvinyl Alcohol–Synthetic Resin Tape
In liver	20	44	43
In spleen	33	28	37
Intrascapular	17	17	28
In abdomen	25	57	33

mandatory in surgical procedures on the hardy rat, a rodent with a large liver and spleen. Of the animal experiments, 90 per cent were accomplished on rats. Application of tincture of iodine and shaving of the abdominal hair was the only operative preparation. In no case was the inserted material itself sterilized.

Though the results in the spleen and intrascapular region were similar, in the liver and abdomen the polyvinyl alcohol film disappeared twice as often as the synthetic resins.

4. Lattes, R., and Frantz, V. K.: Absorbable Sponge Tests, Ann. Surg. 121: 894-896, 1945.

CLOSURE OF TRACHEOTOMY WOUND

A tracheotomy wound in a cat was covered by sticking a small section of the polyvinyl alcohol–synthetic resin tape around the tracheal opening and suturing the skin above. The animal made an uneventful recovery, with a return of normal breathing, and was killed fourteen weeks later. The tracheotomy wound had closed over completely, and no trace of the synthetic adhesive tape was discovered. Microscopic sections showed cartilage regeneration.

CONTROL EXPERIMENTS

Five rats and 5 mice had large sections of their livers removed, with no synthetic adhesive tape covering and no attempt made to stop the bleeding in the liver. Six of the animals succumbed within one hour after abdominal closure and 2 within four hours, another died ten hours later and 1 animal recovered.

STERILIZATION EXPERIMENTS

Autoclaving the polyvinyl alcohol–synthetic resin tape for twenty minutes at 120 degrees C. and 20 pounds (9.1 Kg.) pressure resulted in a change in form of the film structure, a sort of melting-down process. The adhesiveness and elasticity were only mildly altered. It might presumably be possible, with suitable equipment, to retain these essential properties of the tape under steam sterilization.

Experiments on sterilization by irradiation from the ultraviolet lamp, while not conclusive, offered promise.[5] Pieces of polyvinyl alcohol–synthetic resin tape were contaminated with pathogenic microorganisms (Staphylococcus albus and Bacillus subtilis) placed in Petri dishes in suitable culture mediums and exposed to rays from a special ultraviolet filament at varying distances and lengths of time. Although incubated cultures at twenty-four and forty-eight hours were not sterile, there was a marked inhibition of pathogenic growth in the plates exposed to ultraviolet rays as compared to those not exposed to irradiation. It is possible that the plastic tape, while transparent, may interfere with the transmission of the particular ultraviolet rays—a not insurmountable sterilization problem.

COMMENT

Although the preliminary report demonstrated the feasibility of checking hemorrhage in abdominal viscera of animals with synthetic adhesives, none of the tapes used was sufficiently nonirritating to warrant final consideration. It was recognized that cellophane and the rope

5. The sterilamp, supplied by the Westinghouse Electric Company, was used.

stock filler both were the cause of considerable tissue reaction. Neither crude rubber, polyisobutylene nor Buna S appeared satisfactory as an adhesive in bleeding control.

The development, through the cooperation of the Minnesota Mining and Manufacturing Company, makers of Scotch tape, of a synthetic adhesive coated directly onto a polyvinyl alcohol film without an intervening rope stock paper binder is a notable advance in the search for an innocuous adhesive capable of controlling bleeding and of being absorbed.

This thin, transparent substance produced remarkably little visceral tissue reaction in the 10 rabbits and 7 dogs of the first section of the present study. In many instances the material, while apparently halting the bleeding in the liver, was itself not found on autopsy weeks later.

The possibilities of overlooking this transparent material, when still unabsorbed in the abdomen, being realized, a technic was developed for implanting the tape directly inside a pocket incision of the liver and spleen. These organs were selected as representing maximum difficulties in hemostasis. It was also essential to examine separately the tissue reactions of the component parts of this tape structure.

Polyvinyl alcohol $(CH_2CHOH)_x$ is a synthetic product manufactured by the hydrolysis of polyvinyl acetate. It is a ketose between starch and sugar, a white, tasteless and odorless powder dissolving in water, depending on the degree of polymerization. As much as 63 Gm. of polyvinyl alcohol was given daily to dogs by intravenous infusion for twenty-three days by Hueper, Landsberg and Eskbridge,[6] with no appreciable changes at autopsy other than an accumulation of the colloid material in the reticuloendothelial cells of the spleen, liver, kidney and lymph nodes and the formation of atheroma in the large vessels. As in cholesterol atheromatosis, these changes occur only after highly excessive and continuous intravenous administration of polyvinyl alcohol. Hueper[7] found polyvinyl alcohol a relatively inert substance, exerting a definite effect on the coagulation process. In the test tube, with the polyvinyl alcohol blood content more than 3 per cent, an anticoagulant action was produced, caused possibly by mechanical obstruction of the fibrinous network. Hueper also injected as much as 2,700 cc. of a 5 per cent polyvinyl alcohol solution in isotonic sodium chloride solution intraperitoneally, with no more untoward reaction than a temporary hydremia, such as is often observed after acacia injections.

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6. Hueper, W. C.; Landsberg, J. W., and Eskbridge, L. C.: Effects of Polyvinyl Alcohol on Blood, J. Pharmacol. & Exper. Therap. **70**:201-215, 1940.

7. Hueper, W. C.: Polyvinyl Alcohol Atheromatosis in Dog Arteries, Arch. Path. **31**:11-25 (Jan.) 1941.

The synthetic resin adhesive of this tape structure is an acrylic ester. MacKenzie, Sharpless and Millard,[8] Edds [9] and Brown,[10] among others, have demonstrated the minimum tissue reaction to implants of methyl methacrylate in facial and dental reconstructive surgery. Photomicrographs taken three months after these implants showed a surrounding fibrous sheath with no acute inflammatory or necrotic processes. The synthetic resin, acrylic esters—a gummy, extremely adherent material rolled into a ball-like mass—used in the present experiments, was removed directly from the sticky face of the specially constructed polyvinyl alcohol–synthetic resin tape.

According to table 6, the percentage of animals in which synthetic resin implants were found in the liver and spleen is double that in which polyvinyl alcohol was found. The lack of tissue reaction also favors polyvinyl alcohol over the acrylic esters. Apparently, cyst formation often accompanies inplantation of the synthetic resins in the liver and spleen, although the immediately surrounding parenchyma is usually normal. It is possible that these small cysts result from the thick consistency of the implanted ball of synthetic resins—in contrast to the thin film of polyvinyl alcohol. The most pronounced tissue reaction with polyvinyl alcohol occurs when the film curls up into a roll—a tendency of this material. Naturally, the smaller implants cause less reaction, while secondary infection greatly increases the amount of scar.

In the intrascapular implants both the polyvinyl alcohol and the synthetic resins were usually found lying inert in the subcutaneous tissue, surrounded by a thin fibrous capsule and completely devoid of any inflammatory or necrotic process. More rarely a fibrous capsule may encase the polyvinyl alcohol film or the synthetic resin implanted within the peritoneal cavity; abdominal adhesions are not usual. Animals in which the implanted material was not located after careful search at autopsy were still classified under the heading of "not found" rather than "dissolved" because of the possibility of overlooking the thin, transparent film, although it was obvious in the microscopic sections of the livers and spleens that definite autolysis was taking place in the implanted foreign body. Apparently, according to table 6, some enzyme within the peritoneal cavity acts to cause a greater percentage of synthetic adhesive dissolution than with the subcutaneous implants. In the case of the polyvinyl alcohol film, that placed in the liver disappeared more often than that implanted in the spleen. For all three materials—the combined polyvinyl alcohol–synthetic resin tape,

8. MacKenzie, C. M.; Sharpless, D. H., and Millard, P.: Tissue Reactions to Vitallium and Acrylic Implants, Northwest Med. **44**:277-282, 1945.

9. Edds, M. V., Jr.: Prevention of Nerve Regeneration and Neuroma Formation by Caps of Synthetic Resin, J. Neurosurg. **2**:507-513, 1945.

10. Brown, A. M.: Methyl Methacrylate Useful in Facial Corrective Surgery, Arch. Otolaryn. **39**:179-182 (Feb.) 1944.

the synthetic resins alone and the polyvinyl alcohol film—the lowest incidence of disappearance was found with the intrascapular (subcutaneous) procedure.

The question arises, if dissolution of these synthetic adhesives is possible within the body, why has not a greater percentage of these materials disappeared within the experimental animals? At the present time a precise answer cannot be given, although the size, amount and compactness of the implanted material appear as important factors in the possible process of autolysis. Infection also predisposes to nonabsorption, a heavier connective tissue reaction often enclosing a caseous, infected mass. This untoward reaction, in spite of the nonsterilization of the synthetic adhesives, was local and infrequent and abetted by a curling up of the material into a thick lump.

Also, in the manufacture of the polyvinyl alcohol film, small amounts of other chemicals are added as plasticizers to impart certain physical qualities to the synthetic tape. These and other process factors undoubtedly alter tissue insert characteristics. Additional studies to clarify further problems of absorption and bleeding control are now in progress and will be incorporated in a third report, soon to be released.

It is not the intention of the present investigation to offer polyvinyl alcohol or the acrylic esters, in their present stage of development, as suitable for use in the control of bleeding in man. These studies have not as yet reached the clinical trial stage, but the definite absence of parenchymal damage, the paucity of connective tissue stimulation and the complete lack of generalized toxic reactions make it probable that some forms of the synthetic adhesives polyvinyl alcohol and acrylic esters may eventually be incorporated into a plastic tape capable of controlling bleeding within the human body. Of the two substances investigated, polyvinyl alcohol appears considerably more promising, particularly when compared with cellophane, polyisobutylene, Buna S and crude rubber, which produce severe irritation of the tissues.

Among the 252 animals operated on, only 1 death occurred directly as a result of hemorrhage in the liver—that in the animal in which a Buna S adhesive was used. While it is probable that the liver of the rat and rabbit possesses distinct limitation of bleeding properties, the present study appears to verify the previous observation that the synthetic resin (acrylic esters)–polyvinyl alcohol tape controls hemorrhage more satisfactorily than other adhesives investigated to date.

Dissolution of the synthetic adhesives, when it occurs, probably results from leukocytic and enzyme digestion, a process similar to the absorption of ordinary surgical gut. The essential innocuous properties of polyvinyl alcohol and acrylic esters in contact with living cells are demonstrated in the accompanying photomicrographs. Contrast the minimum adjacent tissue reaction in figures 1 to 11 with the marked

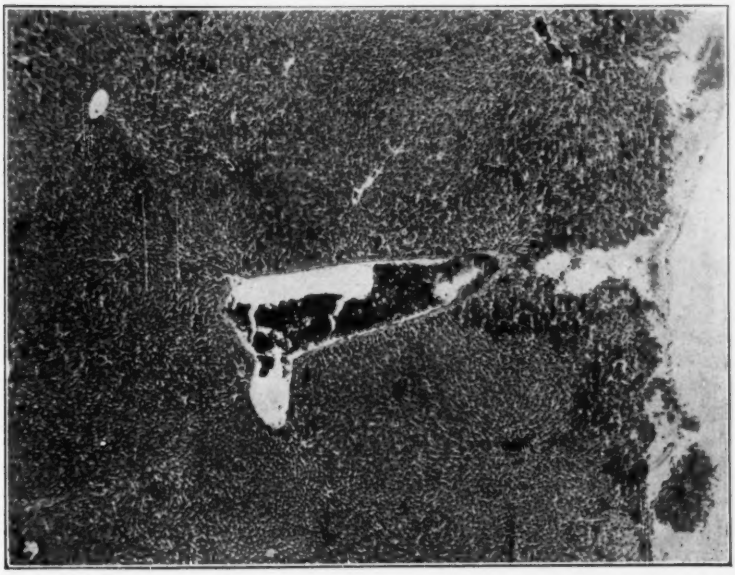

Fig. 1.—Liver of a rat (× 40) twelve weeks after pocket insertion of polyvinyl alcohol film. The plastic material is apparently being dissolved. Surrounding the thin-walled capsule is normal liver parenchyma. Darker-staining, regenerating hepatic cells are in evidence near the cut surface.

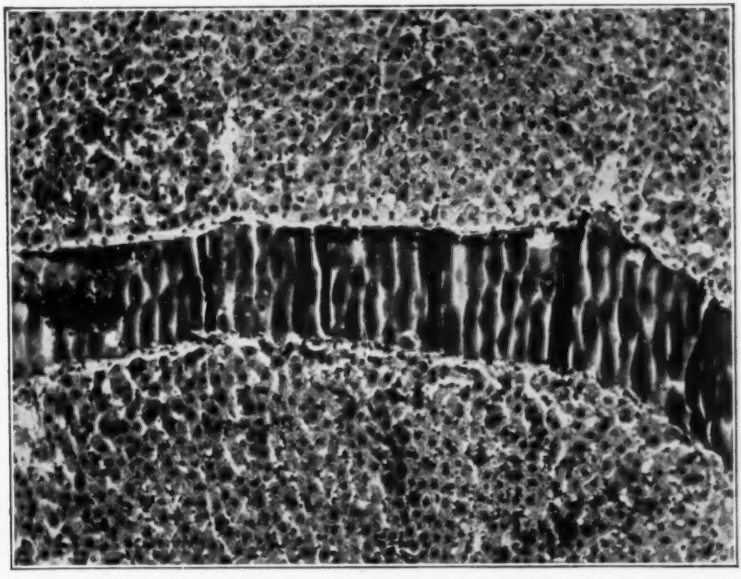

Fig. 2 (× 140).—High power magnification of different area from same rat as in figure 1 twelve weeks after implantation of polyvinyl alcohol film. Note absence of scar tissue reaction surrounding collagenous material, also normal structure of hepatic cells.

Fig. 3 (× 175).—Polyvinyl alcohol film implanted in pocket incision in liver of rat eighteen weeks previously. Two areas of scar remain separated by peninsula of liver tissue. Hepatic structure shows minimum damage.

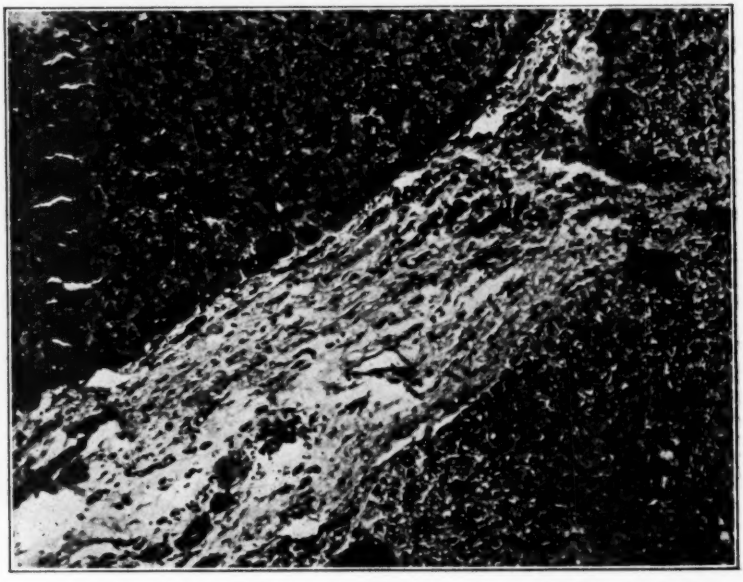

Fig. 4 (× 125).—High power magnification of scar in figure 3 showing invasion of colloid material by leukocytes and fibrous tissue. Note healthy liver parenchyma adjacent to scar.

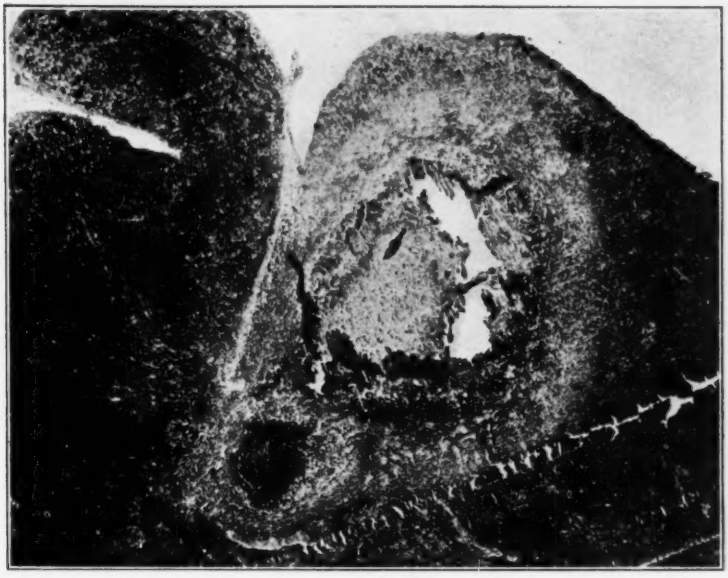

Fig. 5.—Spleen of rat (× 27) fourteen weeks after implanting polyvinyl alcohol film through sandwich incision. Note circular lighter zone of reaction engulfing well of disintegrating material. Lighter scar tissue area blends into apparently healthy splenic pulp.

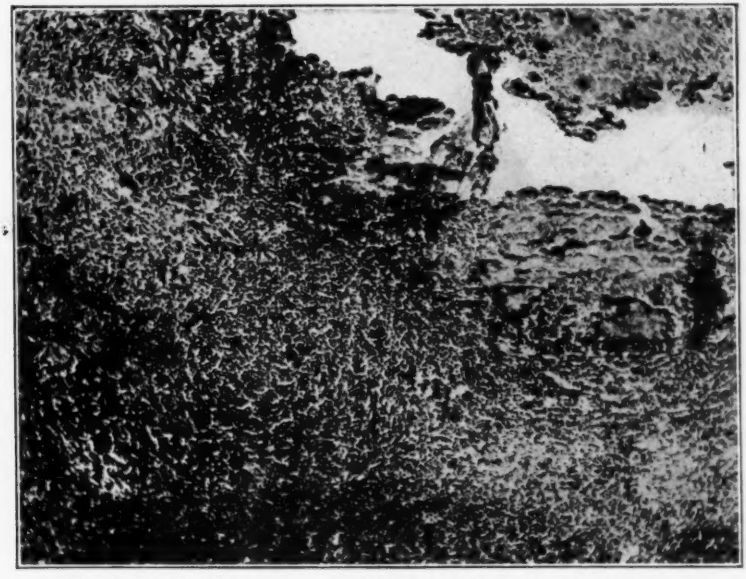

Fig. 6 (× 85).—High power magnification of figure 5. Colloidal material in stage of liquefaction is invaded by zone of leukocytes from surrounding splenic pulp.

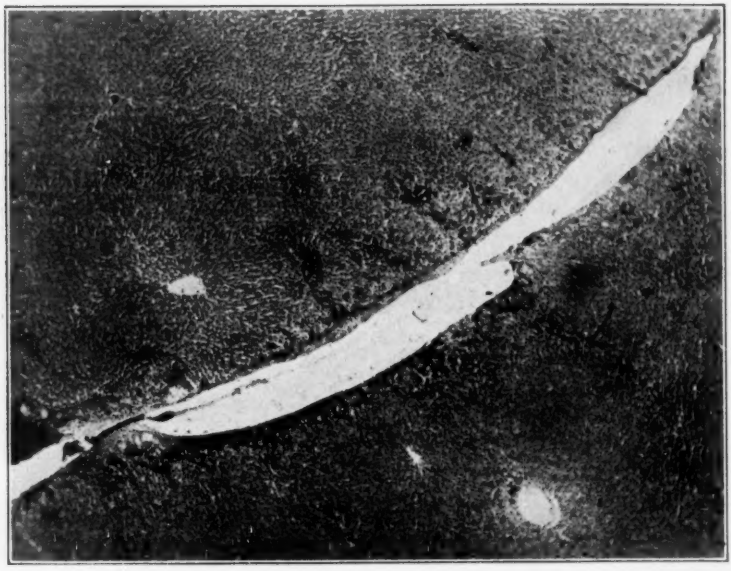

Fig. 7 (× 40).—Synthetic resin implant in liver pocket of rat eighteen weeks previously, showing cyst formation, with mild scar tissue capsule, blending immediately into undamaged liver parenchyma. The synthetic resin material itself is not seen.

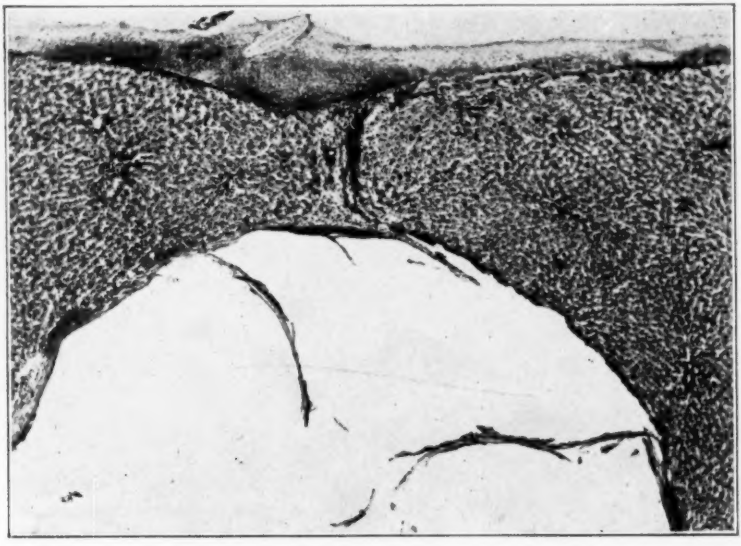

Fig. 8 (× 50).—Cyst resulting from implantation of large globule of synthetic resins in liver of rat fifteen weeks before; thin, scar tissue cyst capsule, with normal liver parenchyma immediately surrounding it. Note original incision scar in middle of hepatic tissue arch. Synthetic resins are not shown. Polyvinyl alcohol–synthetic resin tape has been on liver surface.

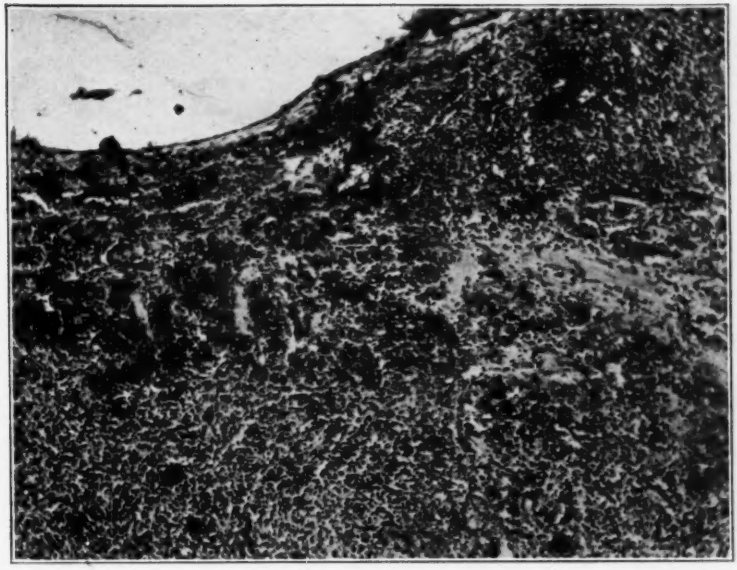

Fig. 9.—Spleen of rat six weeks after transverse incision of spleen and implantation of polyvinyl alcohol–synthetic resin tape, showing edge of cyst, in which tape had been rolled. Note considerable amount of hemosiderin, also small amount of scar tissue capsule in little-affected splenic pulp. Tape itself is not present. × 90.

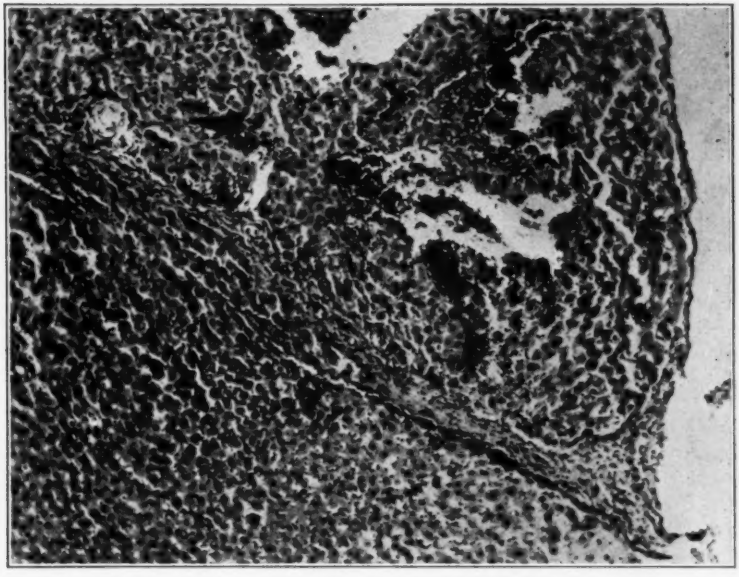

Fig. 10.—Liver of rate (× 125) sixteen weeks after pocket incision and embedding of polyvinyl alcohol film. Note dissolution of material, healed scar and adjacent normal hepatic parenchyma.

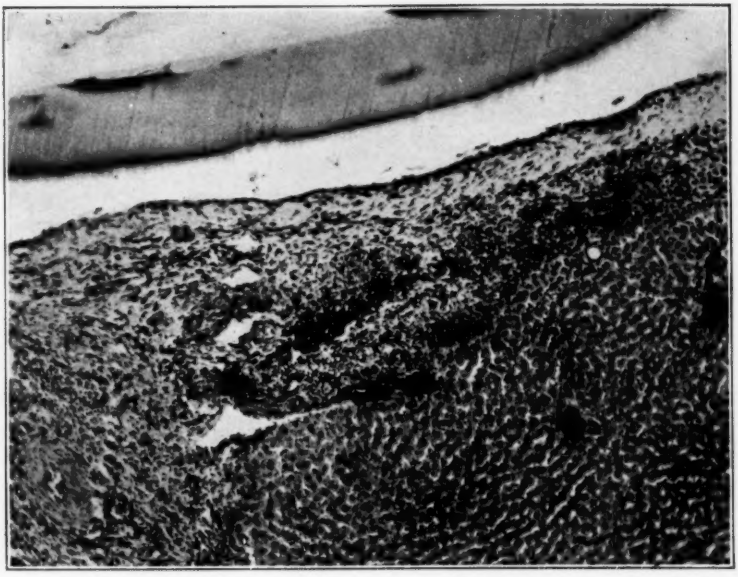

Fig. 11 (× 85).—Edge of liver cyst in rat, showing portion of undissolved polyvinyl alcohol film, which had been embedded in a tight roll fourteen weeks before. Though the scar tissue of this cyst is considerable, the immediate surrounding liver parenchyma is unaffected.

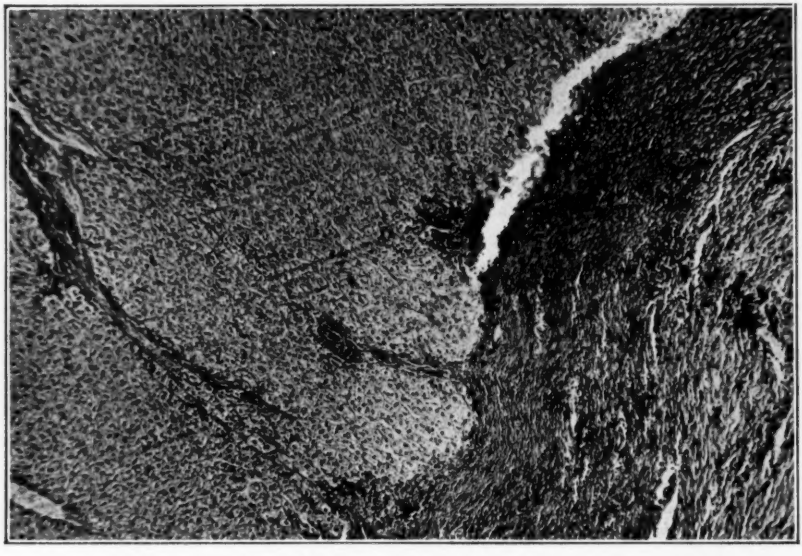

Fig. 12.—Cut of edge of liver of rabbit, with thick scar, from application seven weeks previously of a tape composed of polyisobutylene adhesive, rope stock and cellophane film. Note damage to cytoplasm of liver parenchyma. Contrast with tissue reactions after polyvinyl alcohol or synthetic resin.

inflammatory scar process in figure 12, a cellophane, rope stock, polyisobutylene tape application.

The main significance of the present report, it appears, lies not so much in the percentage of experimental animals in which the implanted synthetic adhesives are not found as in the demonstration that in some cases this plastic foreign body can apparently be absorbed by the tissue juices.

New tape structures and chemical combinations are being developed, in cooperation with the Minnesota Mining and Manufacturing Company, for further investigation. While these studies are additionally encouraging, it would be premature at this time to make such tapes available for surgical experimentation, a field offering unlimited scope for the application of a perfected, hemostatic and absorbable synthetic adhesive.

CONCLUSIONS

Hemorrhage of the liver in dogs, rats and rabbits, produced by surgical extirpation of a large section of the liver, can effectively be controlled by application of analogues in the plastic so-called Scotch tape. The most satisfactory synthetic adhesive, from the standpoint of adhesiveness, control of bleeding and minimum surrounding tissue reaction, is a recently developed transparent tape, consisting of a synthetic resin adhesive (acrylic esters) coated directly on to a polyvinyl alcohol film without an intervening paper binder.

After implantation of the component parts of this tape subcutaneously, intraperitoneally, within the liver and within the spleen, gross evidence of the inserted material could not be found in a percentage of the animals studied. The disappearance, or possible autolysis, occurs somewhat more often with polyvinyl alcohol film than with synthetic resin (acrylic esters). Intraperitoneal disappearance, or absorption, takes place oftener than with subcutaneous implants and apparently is influenced by the length of the time the material is in the body, its size and compactness and the avoidance of infection. Microscopic sections of the liver and spleen reveal the possibility of the polyvinyl alcohol film being absorbed with little scar formation and practically no parenchymal damage. Synthetic resin (acrylic esters) inserts, while nontoxic to tissue, have a tendency, in a compact mass, to cause cyst formation and somewhat more scar formation.

It is not unreasonable to presume that a synthetic adhesive tape, hemostatic, nonirritant to tissues and capable of absorption, can be developed. The manifold possibilities of this perfected tape reveal themselves in all surgical fields. Further animal investigation with

analogous adhesive structures (now in progress), together with a satisfactory method of sterilization, is necessary before these synthetic adhesives are ready for clinical trial.

SUMMARY

1. Ten rabbits and 7 dogs had sections of their livers removed and the gap closed above and below in a plastic adhesive envelope of various analogues of Scotch tape. One rabbit died of hemorrhage and 1 of peritonitis; the rest of the animals recovered and were subjected to autopsy, one to seven weeks later. Reactions in the liver varied from intrahepatic abscess with an undissolved foreign body to a mild fibrous scar, depending on the type of synthetic adhesives used. A tape composed of a synthetic resin (acrylic esters) adhesive on a polyvinyl alcohol film without a paper binder caused the minimum of tissue reaction. At the end of four weeks none of these tapes had dissolved in the test tube either in human gastric juice or in human blood serum.

2. Of 10 control rodents with no synthetic adhesives over the sectioned liver, 6 succumbed one hour after abdominal closure and 2 within four hours; another died ten hours later and 1 animal recovered.

3. In a series of 235 animals (rabbits, mice and rats) the synthetic resins (acrylic esters), the polyvinyl alcohol film and the synthetic adhesive tape combination (the two plastics together) were separately implanted within the liver, within the spleen, intra-abdominally and subcutaneously. At intervals from one week to eight months later the recovered animals were subjected to autopsy and the tissues studied microscopically.

The number of animals in which the synthetic resin was not found was 17 per cent for the subcutaneous application and 26 per cent for application within the peritoneum (average for liver, spleen and intra-abdominal implants). With polyvinyl alcohol film inserts, the numbers were 17 and 43 per cent. For the combined polyvinyl alcohol–synthetic resin tape the percentages were 28 and 38.

Microscopic sections revealed no decided parenchymal damage in the liver or spleen from synthetic resin or polyvinyl alcohol implants. Scar tissue reaction was minimum, particularly with polyvinyl alcohol, although cyst formation was found with compact synthetic resin inserts. In numerous cases the material seemed to have been dissolved.

Factors apparently influencing absorption are size, weight and compactness of inserts, length of time, place of implant and avoidance of infection.

4. Sterilization of the tape may be accomplished by ultraviolet irradiation rather than autoclaving.

5. While the present synthetic resin–polyvinyl alcohol plastic tape cannot yet be recommended for clinical studies in man, there are encouraging probabilities for the early development of a satisfactory synthetic adhesive tape hemostatic, nonirritating to tissues and completely absorbable within the body.

Many officers and enlisted men of the United States Army and Navy Medical Corps and members of the University of Utah, University of Oregon and the University of Southern California Medical Schools assisted in this work.

Part of the study was carried on in the laboratories of the Department of Pharmacology and Toxicology, University of Southern California Medical School.

MULTIPLE PRIMARY TUMORS WITH FIBROSARCOMA AND COEXISTING CARCINOMA OF THE LUNG

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DAVID GRAYZEL, M.D.
SAMUEL L. BERSON, M.D.
AND
SOLOMON ROSENBERG, M.D.
BROOKLYN

THE INCIDENCE of multiple primary tumors is low. Slaughter,[1] confirming the impression of Warren and Gates,[2] stated that cases of multiple primary malignant growths represent 3.9 per cent of all cases of cancer. Primary sarcoma of the lung constituting one of these tumors is even less common. Primary carcinoma of the lung, on the other hand, is by no means an uncommon disease—constituting about 10 per cent of all cases of cancer seen at necropsy—and is occasionally seen in instances in which two primary cancers coexist in the same person. The occurrence of a primary carcinoma of the lung in a patient who has a primary sarcoma of that organ with another benign tumor of the contralateral lung is extremely rare. It is even rarer to find such a state further complicated by several benign tumors in other organs.[3] The case to be reported is an example of multiple neoplastic tumors.

REPORT OF A CASE

I. S., a 55 year old white woman entered The Jewish Hospital of Brooklyn on Aug. 19, 1947, complaining of a chronic cough of ten years' duration. In recent months the cough had become more severe and more disturbing, especially during the early part of the day. About four months prior to the patient's admission to the hospital the sputum became streaked with blood. This gradually subsided and was followed by a change from the heretofore nonproductive cough to one productive of a mucoid sputum, which later became mucopurulent in

From the departments of thoracic surgery and pathology, Jewish Hospital of Brooklyn.

1. Slaughter, D. P.: The Multiplicity of Origin of Multiple Tumors, Internat. Abstr. Surg. **79**:89, 1944.

2. Warren, S., and Gates, O.: Multiple Primary Malignant Tumors, Am. J. Cancer **16**:1358, 1932.

3. Hochberg, L. A.: Primary Carcinoma of the Lung, to be published.

character. A roentgenogram of the chest taken one week before her entrance to the hospital revealed a "well circumscribed opacity of the left upper lobe," interpreted as a "lung cyst or a degenerative process." The patient's past history was not remarkable, except for a hysterectomy in 1945 for "fibroids of the uterus."

Examination revealed an apparently healthy vigorous middle-aged woman, whose blood pressure was 132 systolic and 88 diastolic and whose temperature, pulse and respirations were normal. On the abdomen there was a well healed

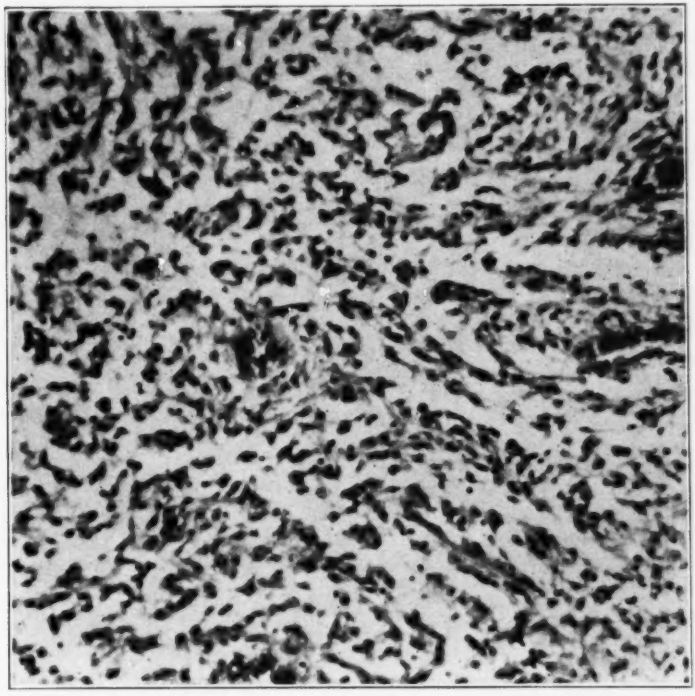

Fig. 1.—Fibrosarcoma of the lung (× 200).

right suprapubic scar. There was some dulness to percussion over the upper third of the left side of the chest posteriorly, in which region the breath sounds were absent, especially opposite the second dorsal vertebra. The examination was otherwise noncontributory.

A roentgenogram of the chest was interpreted as containing a "circular tumor involving the upper half of the left lung field . . . possibly not a bronchogenic carcinoma but one of the neurofibromatous group . . ."

The hemoglobin content was 90 per cent, the red blood cell count 4,420,000, and the white blood cell count 11,450, with a differential count of 65 per cent

polymorphonuclear cells, 8 per cent band cells, 7 per cent lymphocytes, 19 per cent eosinophils and 1 per cent monocytes. The sedimentation rate was 10 mm. in an hour. Urinalysis showed a faint trace of albumin and an occasional white blood cell per high power field. The blood urea nitrogen was 17.8 mg. per hundred cubic centimeters, and the blood sugar was 112 mg. The reaction to the Kline test was negative. The sputum contained Streptococcus viridans, Micrococcus catarrhalis and diphtheroids. Tubercle bacilli were not present in the sputum. The electrocardiogram was within normal limits.

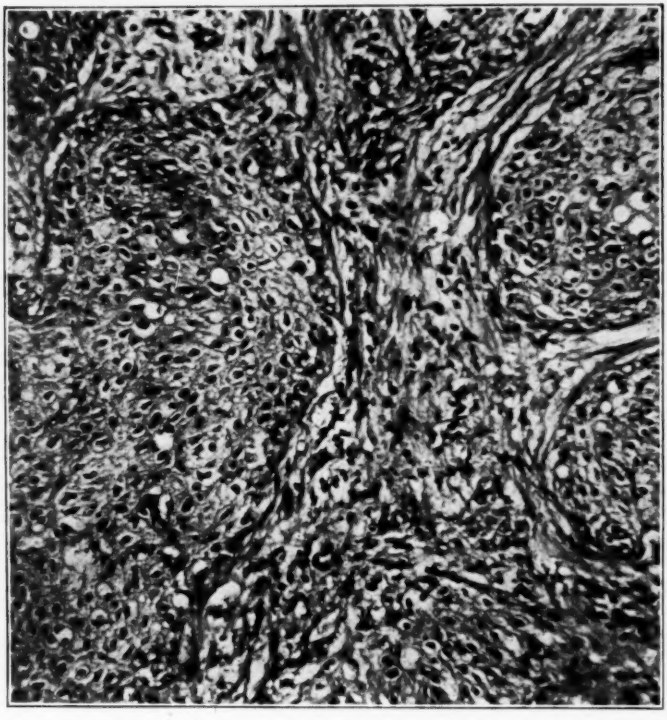

Fig. 2.—Fibrosarcoma of the lung with coexisting epidermoid carcinoma (× 200).

On August 22, the third hospital day, thoracotomy was performed on the left side under general anesthesia. A large mass was found in the upper lobe. The neoplasm was attached to the anterior wall of the chest and to a lesser extent to the distal part of the transverse part of the aorta. There were no nodes in the mediastinum. The upper lobe of the left lung was removed by individual ligation and suture of the vessels and bronchus. During the operation the blood pressure and pulse rate varied considerably, but they were essentially

normal at the end of the procedure. At no time was there any impairment of respiration. When the patient was returned to her room, the blood pressure, pulse and respiratory rate were not remarkable. However, she did not regain consciousness. The transfusion started during the operative procedure was continued in the patient's room. About five hours after the patient was returned to her room she was still unconscious, breathing with some difficulty. About 11 p. m. (twelve hours postoperatively) she was still unconscious, the temperature was 104.2 F. and the respirations were easier and regular. Five hours later the

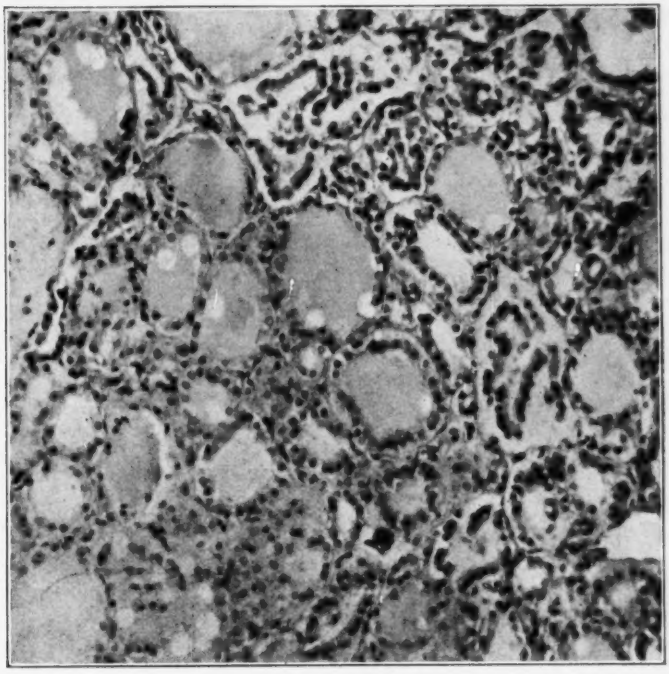

Fig. 3.—Colloid adenoma of the thyroid (× 200).

temperature rose to 106.4 F., the pulse rate rose to 140 per minute and was thready and the respiratory rate rose to 52 per minute and occasionally was Cheyne-Stokes in character. The patient died seventeen hours after completion of the operation never regaining consciousness.

Surgical Specimen.—The surgical specimen consisted of the upper lobe of the left lung. It was pinkish gray, measuring 23.0 by 11.5 by 6.0 cm. It was soft and noncrepitant. Projecting above the surface and within the substance of the lung there was a firm, pinkish yellow irregular mass 11.5 by 10.0 by 5.0 cm., which was sharply demarcated from the adjacent lung tissue. The cut surface

of the mass was soft and yellowish pink, with a hemorrhagic center. A secondary bronchus could be seen leading into the tumor mass. Tumor tissue was also present in the large veins. Microscopic examination of the mass showed a varied picture. The tumor consisted of spindle-shaped cells, varying in size, with ovoid or round vesicular nuclei; some of the cells were hyperchromatic, and an occasional cell was in mitotic division. The cells were arranged in intertwining bands or in whorls. The stroma was vascular and contained many foci of extravasated blood. With Laidlow connective tissue and Mallory stains, the tumor

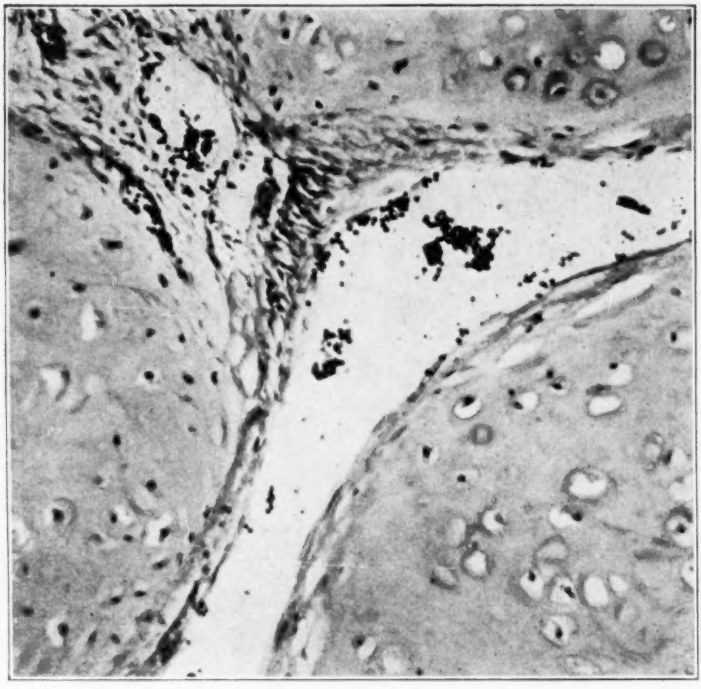

Fig. 4.—Chondroma of lung (× 200).

was seen to contain a great deal of collagen arranged in dense bands in some areas and in a fibrillary fashion in others. Intermingled with these cells there were nests of large ovoid or polygonal cells of varying size and shape. Some of these cells were seen within endothelium-lined spaces.

Diagnosis.—The diagnosis was fibrosarcoma and carcinoma of the upper lobe of the left lung (figs. 1 and 2).

Observations at Autopsy.—The body was that of a well devoloped, obese, middle-aged white woman. A 30 cm. semilunar recent surgical incision was present on the left hemithorax, extending along the sixth rib from the costochondral junction

to the vertebra. A 13 cm. old right rectus scar was present in the lower part of the abdomen. About 100 cc. of dark red blood was present in the left pleural cavity. The hilar vessels were snugly tied, and the remains of the bronchus to the upper lobe of the left lung were closed securely by several interrupted black silk sutures. The edge of the liver projected 8 and 4 cm. below the right and midcostal margins respectively.

The thyroid contained a small firm yellowish nodule at the periphery. On cut section it was yellowish and faintly lobulated, measuring 1.1 cm. in diameter.

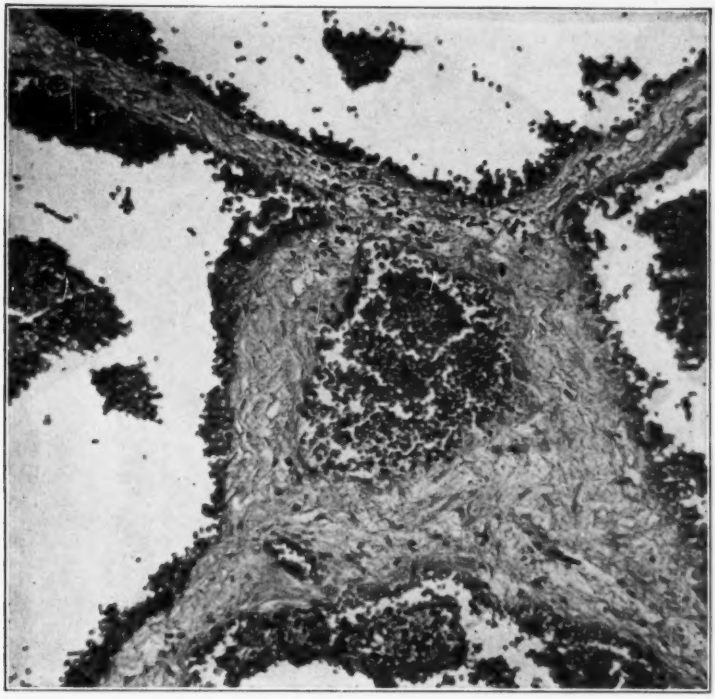

Fig. 5.—Cavernous hemangioma of liver (× 200).

Microscopically this nodule consisted of several discrete, well circumscribed oval masses of thyroid tissue in which the colloid took a dark pink stain and the acini were small and rudimentary (fig. 3). The remainder of the gland was not unusual.

The right lung weighed 423 Gm. and was well aerated. A hard white firm nodule, 2.1 cm. in diameter, was present at the periphery of the middle lobe. On section this nodule was gray-white and delineated from the surrounding parenchyma. Microscopic examination revealed irregular masses of light pink and

dark purple cartilaginous tissue having poorly stained nuclei. Separating these cartilaginous areas were thin and broad areas of adipose tissue, primitive cuboidal cell-lined ducts with many desquamated lining cells, loose mucoid tissue with many fibroblasts and light pink hyaline zones and many congested thin-walled vessels (fig. 4).

The liver weighed 2,240 Gm. At its extreme right and on the diaphragmatic surface there was a large dark blue lobulated area, 9.0 by 11.0 by 5.0 cm., which on section consisted of dark-bluish red areas traversed by thick white fibrous

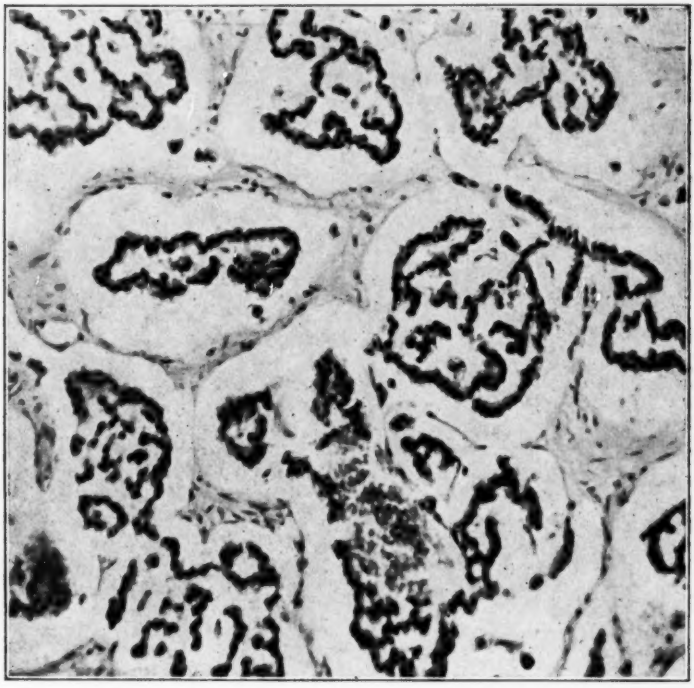

Fig. 6.—Nesidioblastoma of pancreas (× 200).

strands. A similar, although smaller, area was found at the posterolateral extremity of the left lobe of the liver. Microscopic examination of these two areas showed large and small irregular cystic spaces, congested with lymphocytes and lined by prominent endothelium. Separating the cystic spaces were broad septums composed of loose collagenous tissue with many areas of hyalinization (fig. 5). The zones were distinctly demarcated from the hepatic parenchyma.

The pancreas weighed 150 Gm. and grossly was not remarkable. Microscopic examination, however, revealed an isolated, well encapsulated zone of atypical tissue within otherwise normal pancreas. This tissue had a loose light pink

reticulum encompassing vacuolated spaces in which could be seen irregular cords, in linear arrangement, containing dark-staining nuclei and light purple homogeneous cytoplasm (fig. 6). Many cords had united to form glandular structures which showed hyperplasia of the epithelial lining.

The spleen weighed 365 Gm. At the periphery there was a dark bluish area, 2 cm. in diameter, which was firmer than the adjacent splenic tissue and distinctly demarcated from it. Microscopically this tissue consisted of cystic spaces containing a dark homogeneous material and many erythrocytes. The lining of these

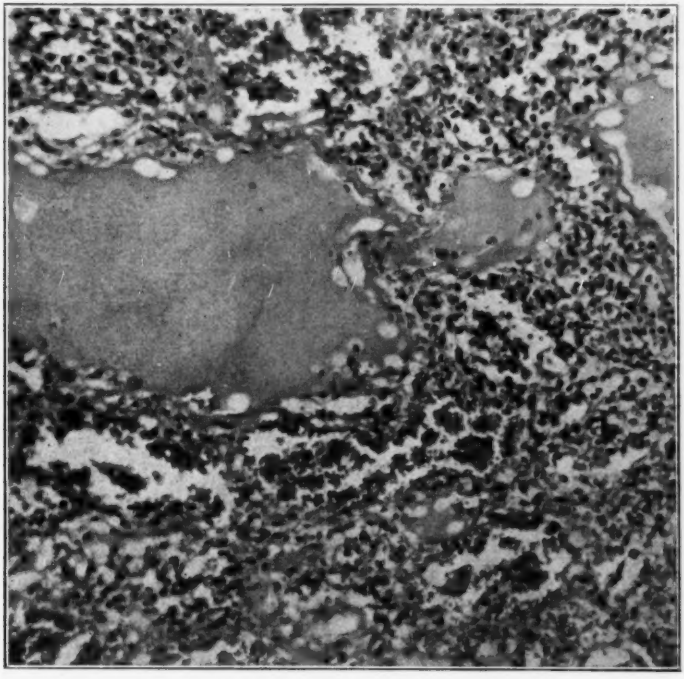

Fig. 7.—Cavernous hemangioma of spleen (× 200).

spaces was not clearly defined (fig. 7). The cystic tissue merged gradually with the normal splenic tissue. One vessel within the spleen contained a prominent tumor thrombus consisting of fibrosarcomatous elements.

The right adrenal gland presented nothing unusual. The left adrenal gland was almost completely replaced by fibrosarcomatous tissue.

Both kidneys presented severe nephrosis and contained fibrosarcomatous thrombi in many arteries.

Tumor thrombi were also found in the left internal carotid and left middle cerebral arteries.

Examination of the slides of the uterus removed two years previously showed leiomyomas (fig. 8). There was no evidence of cancer in any of the slides.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: Excision of the upper lobe of the left lung; fibrosarcoma and carcinoma of the lung; fibrosarcomatous metastasis to adrenal gland and left periadrenal tissue; fibrosarcomatous thrombi in the arteries of the spleen, kidneys and brain; arteriosclerosis of cerebral vessels with recent tumor thrombi in the left internal carotid and left middle

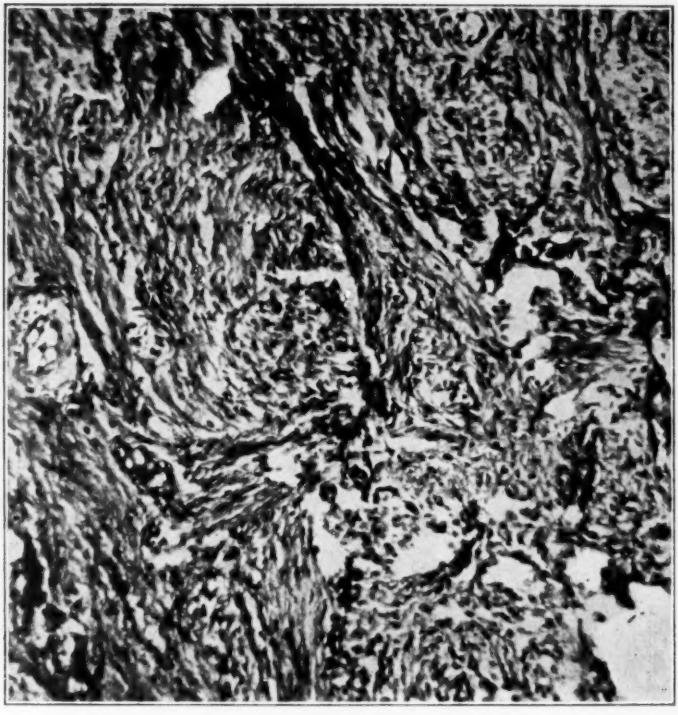

Fig. 8.—Leiomyomas of uterus (× 200).

cerebral arteries; recent infarction of the left internal capsule, left globus pallidus and pons; hepatitis and cirrhosis of the liver; nephrosis; edema of the brain; congestion of the viscera; chronic pneumonitis of the right lung; arterial nephrosclerosis; colloidal adenoma in the thyroid; chondroma in the right lung; cavernous hemangiomas of the liver; cavernous hemangioma in the spleen; nesidioblastoma of the pancreas; diverticula and adenomatous polyp of the descending colon; scar of hysterectomy [for leiomyomata uteri] with fibrous peritoneal adhesions, and follicular cysts in the right ovary.

SUMMARY

An unusual case of multiple tumors is presented. Besides carcinoma and fibrosarcoma of the left lung, tumors were found in six organs. Five of the benign lesions were asymptomatic, and the sixth gave rise to symptoms necessitating a hysterectomy. The malignant tumor gave rise to symptoms requiring a pulmonary lobectomy.

The susceptibility to tumor formation exhibited by this patient seemed to be more than a mere coincidence. Perhaps she truly was endowed with a "tumor diathesis."

INTRA-ARTERIAL ADMINISTRATION OF PENICILLIN WITH SPECIAL REFERENCE TO BONE MARROW CONCENTRATION

An Experimental Study

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AND
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NEW YORK

THE RATIONALE of the intra-arterial injection of antiseptic substances was formulated by Parlavecchio [1] in 1899. From his experimental observations he concluded that the procedure was a feasible method of obtaining a high concentration of therapeutic agent in a diseased tissue. In his report he suggested that the presence of a peripheral capillary field, in addition to the pulmonary circuit, through which a substance so injected must pass before it could reach the brain and other viscera, tended to minimize any toxic effect.

These assumptions have formed the logical basis for the sporadic clinical reports that have since appeared. The advent of penicillin served as a stimulus to trial of this technic. In 1944, Ribeiro [2] treated a patient with purulent osteoarthritis of the knee by repeated injections into the femoral artery. At the same time, Gudin and Neiva Filho [3] successfully treated 2 patients with osteomyelitis who previously had not responded to intramuscular administration of penicillin. In 1945, Glasser and associates [4] and, in 1946, Shaffer [5] reported the effects of arterially injected penicillin on inflammatory and vascular processes of the extremities.

From the Division of Bacteriology, Laboratories of the Mount Sinai Hospital.

1. Parlavecchio, G.: Sul lavaggio antisettico interstiziale dei tessuti dalla via arteriosa, Policlinico (sez. prat.) **6**:66-74 (Feb.) 1899.

2. Ribeiro, E. B.: Penicilina por via arterial, Bol. San. São Lucas **6**:19-20 (Aug.) 1944.

3. Gudin, M., and Neiva Filho, A.: Tratamento da osteomielite por asepsia integral e penicilina intra-arterial, Mem. Inst. Oswaldo Cruz **41**:163-166 (Aug.) 1944.

4. Glasser, S. T.; Herrlin, J., and Pollock, B.: Intra-Arterial Injection of Penicillin for Infections of the Extremities, J. A. M. A. **128**:796-802 (July 14) 1945.

5. Shaffer, J. O.: Intra-Arterial Penicillin Therapy for Infections of the Extremities, Minnesota Med. **29**:928-932 (Sept.) 1946.

While these clinical experiences imply confirmation of the principles involved, there is lacking a quantitative estimation of the concentration of penicillin in the tissues after the injections. The experiments reported here were designed to study the comparative local levels of penicillin after various methods of administration. Because of its clinical significance, bone marrow was the tissue selected for assay.

EXPERIMENTAL STUDY

Young male dogs were employed throughout, with the exception of 2 older dogs to be noted later. The animals were anesthetized by the intravenous injection of veterinary pentobarbital sodium. The dose was 0.5 cc. per kilogram of body weight, and if necessary more was administered during the operation.

Operation.—The tibia and femur of one side were exposed, great care being exercised not to injure the nutrient arteries of the bones. The cortical layer of the presenting surfaces was then chiseled off. Free bleeding, indicating an intact blood supply, was noted in the marrow cavity. The femoral artery on the same side was isolated for injection. Commercial penicillin, 10,000 units per cubic centimeter in isotonic solution of sodium chloride, was injected in the amounts and by the routes and methods indicated in the tables. The intravenous injections were made into the ear vein and the intramuscular injections were given into the pectoral muscle. The intra-arterial injections were made into the femoral artery on the same side as the exposed bones, under direct vision in order for us to be certain that the entire amount was delivered into the lumen. After the intra-arterial injection, bleeding stopped almost immediately after slight pressure, provided that the femoral artery was not denuded of its sheath. When two injections were given, either a twenty or a thirty minute interval was allowed, as indicated in table 2.

Specimens of bone marrow were obtained at the periods indicated. Immediately before the specimens were taken by means of a mastoid curet, bleeding in the marrow cavity was momentarily stopped by compression with dry gauze. We were extremely careful to procure true bone marrow, rather than clotted blood or seepage, for penicillin assay. One half of each specimen was from the femur and the rest from the tibia, so that each specimen represented combined femoral and tibial marrow. The first specimen was taken from the central portion of the marrow cavity, and subsequent periodic samples were obtained from sites in a progression toward the epiphysial plate in order that the vascular architecture and blood supply of the later specimens should be disturbed as little as possible.

The operation and the collection of specimens were performed under strictly aseptic conditions.

Penicillin Assays.—Each specimen of bone marrow was suspended in distilled water in a concentration of 50 mg. per cubic centimeter. After the marrow had been crushed by means of a solid glass rod, the samples were controlled for sterility in a 1 per cent dextrose broth containing penicillinase and were placed in the freezing compartment of the refrigerator overnight. Contaminated specimens were filtered through a Seitz filter. The following day, after being permitted to thaw out, the marrow suspensions were agitated vigorously and then centrifuged at 3,000 revolutions per minute for twenty minutes. Assays for penicillin were made on the supernatant fluids.

The method employed in this laboratory is a broth tube dilution method with Staphylococcus aureus H used as the test organism and fresh meat extract broth as the medium. The minimal concentration of the standard penicillin required to inhibit the inoculum of 5×10^2 Staph. aureus H cells was 0.02 unit

TABLE 1.—*Levels of Penicillin in the Bone Marrow of Dogs After Single Injections of Penicillin by Various Routes*

Dog	Weight (Kg.)	Route of Administration	Dose (Units/Kg.)	Levels of Penicillin in Bone Marrow (Units/Gm.) 10 Min.	20 Min.	30 Min.	60 Min.	120 Min.	180 Min.
1	19.2		2,000	4.0	...	2.0	0.8	<0.8	0.8
2	12.5		2,000	1.32	0.8	0.88	0.8	<0.8	...
*3	14.5	Intra-arterial	2,000	2.0	0.5	<0.5	1.3	...	...
*4	22.0		4,000	4.0	4.0	4.0	2.0	2.0	<0.8
5	15.0		4,000	8.0	...	1.98	1.0	...	...
1	19.2		2,000	2.0	<0.8	...	<0.8	...	...
6	9.2		2,000	10.0	1.32	1.0	1.0	1.0	...
7	16.0		2,000	0.5	<0.4	...	0.5	...	...
*8	15.6	Intravenous	4,000	1.0	1.0	0.8	<0.8	<0.8	<0.8
*9	14.5		4,000	<0.8	0.8	0.8	<0.8	<0.8	0.8
*10	14.2		4,000	10.0	8.0	2.0	<0.8	0.8	...
*11	14.6		4,000	0.8	4.0	2.0	0.8	...	...
*12	12.2		4,000	1.0	4.0	<1.0	<1.0	...	...
*16	10.6	Intramuscular	4,000	<1.0	<1.0	1.14	1.0	...	...
17	11.8		4,000	1.0	0.8	<1.0	1.0	...	...

* Refer to table 2.

TABLE 2.—*Levels of Penicillin in the Bone Marrow of Dogs After Two Injections of Penicillin by Various Routes, 2,000 Units per Kilogram of Weight Being Given at Each Injection*

Dog	Weight (Kg.)	Route of Administration	Levels of Penicillin in Bone Marrow (Units/Gm.) 10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	80 Min.	90 Min.	150 Min.
*4	26.0	Intravenous	2.0	4.0	1.14	↓8.0	4.0	4.0	...	...	2.0
15	18.7	and	<0.5	<0.5	↓2.0	1.0	<0.5	...	<0.5	...	...
*12	11.6	Intravenous	2.6	1.6	↓4.0	...	1.32	...	1.0	...	...
		Intramuscular									
*16	10.5	and	1.98	<1.32	↓<1.0	<1.0	...	...	...	...	...
18	10.2	Intra-arterial	<1.0	<1.0	↓<1.0	<1.0	1.0	...	<1.0	...	...
*8	19.0		2.0	0.8	1.0	↓4.0	...	1.32	...	<0.8	<0.8
*10	14.0	Intra-arterial	4.0	4.0	0.88	↓13.2	4.0	0.8	...	0.8	<0.8
*9	14.5	and	<0.8	<0.8	...	↓<0.8	<0.8	...	...	...	<0.8
13	20.0	Intra-arterial	4.0	4.0	↓10.0	...	1.0	...	1.0	...	...
14	8.5		<1.0	<1.5	↓8.0	<1.0	...	...	...	...	...
19	12.3		0.8	1.32	...	↓13.2	10.0	...	...	...	...
20	15.7	Intravenous	4.0	2.0	0.8	↓10.0	4.0	2.0	...	2.0	1.32
*11	14.5	and	0.88	<0.8	0.88	↓13.3	0.65	<0.88	...	1.44	0.88
*3	13.3	Intra-arterial	4.0	1.32	↓16.0	8.0	<1.0	...	...	...	...
21	9.7		<1.0	1.32	↓11.4	4.0	1.14	...	<1.0	...	...
18	9.6		<1.0	<1.0	↓8.0	2.6	<1.0	...	...	...	...

* Refer to table 1.
↓ Indicates time of second injection.

per cubic centimeter. The standard penicillin was obtained from the United States Department of Agriculture. All titrations of the bone marrow suspensions were accompanied by and compared with this standard.

Results.—The results were divided into two groups. In table 1 are listed the results following single injections of penicillin by way of arterial, intravenous and muscular routes. Table 2 includes the data obtained

after two consecutive injections had been given by these same routes. It may be noted that the penicillin levels of the bone marrow varied in different dogs with the same doses, routes and methods of administration, an indication that considerable individual variation existed. The highest peak levels usually occurred ten minutes after an injection.

With single injections, bone marrow levels were higher after intravascular (intravenous or intra-arterial) administration than after intramuscular administration. Definite, consistent differences between the intravenous and the intra-arterial routes could not be demonstrated.

When two injections of 2,000 units per kilogram each were given twenty or thirty minutes apart, a conspicuous elevation in the concentration of the drug in the bone marrow was noted after the second

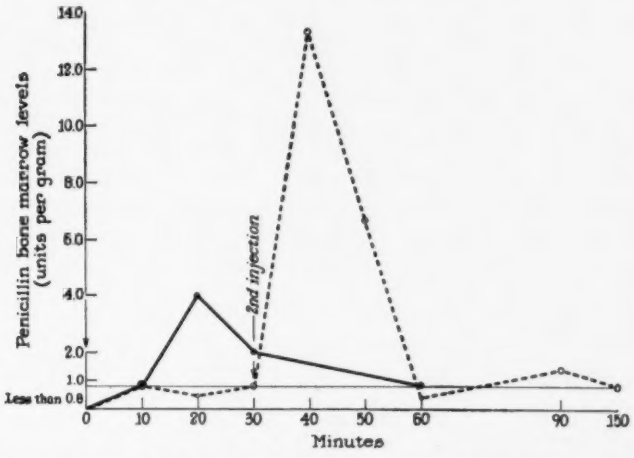

Chart 1 (dog 11).—The solid line indicates the levels of penicillin in the bone marrow after the intravenous administration of 4,000 units per kilogram; the line of dashes, the levels after an injection of 2,000 units per kilogram administered intravenously, followed by an intra-arterial injection of 2,000 units per kilogram of body weight.

injection. This level exceeded by far that found after a single injection of the same total amount of penicillin. The marrow of all dogs which received an intra-arterial dose after a preliminary intravenous injection showed this distinct rise in concentration of the drug. Three of 5 dogs given two consecutive intra-arterial injections also showed considerable elevation in the concentration of penicillin in the marrow. If the two injections were both given by the intravenous route, some elevation of the level of penicillin in the bone marrow was seen, but the rise was not so pronounced as the increases following the other means of administration. Thus, in almost every instance, a noticeable increase in the

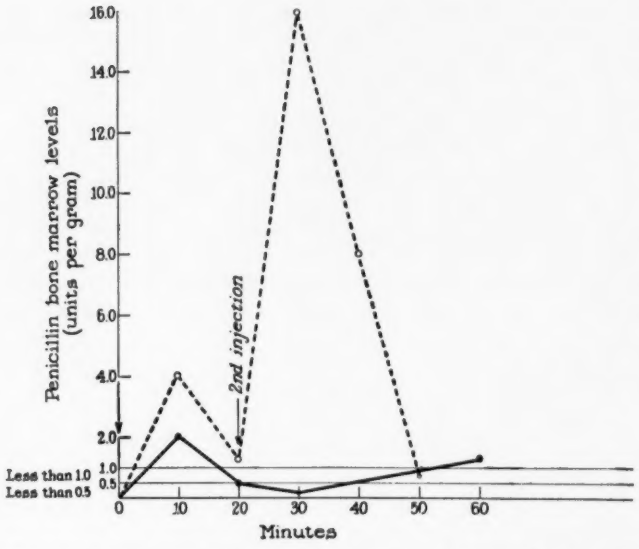

Chart 2 (dog 3).—The solid line indicates the levels of penicillin in the bone marrow after the intra-arterial administration of 2,000 units per kilogram; the line of dashes, the levels after an intravenous injection of 2,000 units per kilogram, followed by an intra-arterial injection of 2,000 units per kilogram of body weight.

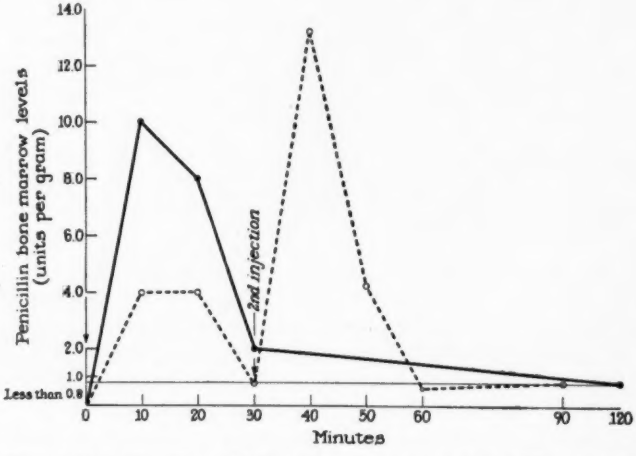

Chart 3 (dog 10).—The solid line indicates the levels of penicillin in the bone marrow after the intravenous administration of 4,000 units per kilogram; the line of dashes, levels after an intra-arterial injection of 2,000 units per kilogram of body weight, followed by another intra-arterial injection of the same amount.

concentration of penicillin in the bone marrow occurred whenever a booster intra-arterial injection was given after a priming intravascular dose. It may also be noted that an intramuscular followed by an intra-arterial injection failed to produce any significant elevation.

After the animals' recovery, the operation was repeated on some dogs, the intact side being used. In this way, comparative observations on different doses, routes and methods of administration could be made in the same dogs. The data are illustrated in charts, 1, 2 and 3. As may be seen from chart 1, a preliminary intravenous injection followed by an intra-arterial injection produced a considerably greater concentration of penicillin in the marrow than did the same total dose administered as a single intravenous injection. Similar elevations resulting from booster arterial injections are illustrated in charts 2 and 3.

Individual variation is best illustrated by a comparison of the results of experiments on dogs 9 and 10. It may be noted that in dog 9, even after two arterial doses, little or no penicillin could be found in the marrow, although an assay of the blood showed a level of 2.0 units per cubic centimeter thirty minutes after the second injection. This animal was one of our older dogs, and it was believed that age and its effect on the vasculature might account for these findings. By comparison, dog 10, also an old animal, showed very satisfactory levels after the two arterial injections. Both dogs weighed about the same and had received approximately the same dose by the same routes and methods; yet their experimental results were completely at variance. Many factors, such as different vascular patterns in the bone and barriers through which the penicillin must penetrate, may account for this apparent discrepancy. Variations in systemic absorption, diffusion and excretion in different animals may also play a part.

Finally, after analyzing our results for any differences in the duration of penicillin levels in the marrow after various routes and methods of administration, we were unable to note any clearcut differences, since considerable variation in this respect also existed.

COMMENT

It has been demonstrated that in normal young dogs a decided elevation in the concentration of penicillin in the bone marrow results from a priming intravascular injection of the drug, followed by a booster intra-arterial dose. This level is considerably greater than that obtained after a single injection of the same total amount irrespective of the route of administration. Since the degree of diffusion of an antibiotic substance like penicillin is proportional to its concentration, it is logical to assume that if a higher concentration can be achieved greater diffusion of the drug through the marrow cavity will result. Rather poor results

have been reported with penicillin alone in the treatment of chronic osteomyelitis. Robertson [6] stated that long-standing sepsis involving the bone must be considered an unfavorable field for treatment with penicillin administered either locally or systemically. On the other hand, Key [7] has reported that this agent, in conjunction with the proper surgical treatment, has been found a useful adjunct to therapy. According to Buchman and Blair,[8] who described the pathology of the disease, the unfavorable results may be attributed to the poor blood supply and the avascular contents of the diseased marrow, which is therefore beyond the reach of any therapeutic agent carried by the blood stream. In the light of our experimental findings with booster intra-arterial injections, it is believed that higher penicillin levels in the bone can be obtained by this method than with the others aforementioned, and that greater penetration will be favored thereby. The organisms responsible for chronic osteomyelitis are, as a rule, sensitive to the antibiotic; and if they are reached by a sufficient concentration of the drug, a better therapeutic result should ensue. Gerber, Shwartzman and Baehr [9] demonstrated a greater penetration of penicillin into foci of infection when higher peak levels in the blood were produced. In the same manner, greater diffusion and penetration into a focus of infection inside a bone should result if higher concentrations of the drug in the marrow cavity were achieved. For this reason, and because of our experimental results, it is believed that a clinical trial of the method of booster arterial injection in the treatment of osteomyelitis is justified.

A review of the literature reveals that the limited use of this method is directly attributable to the previous absence of an effective, safe antiseptic agent. At the outbreak of World War I, Heddaus [10] successfully treated 6 patients with tetanus by the intracarotid injection of antitoxin. He stated that Leriche had preceded him in this technic by several months. In the same year (1914) the Fiolles [11] suggested the infusion of oxygenated fluid into the major arteries of the extremities infected

6. Robertson, I. M.: Penicillin in Bone Infections, Brit. M. J. **1**:519-521 (April 15) 1944.

7. Key, J. A.: Penicillin and Sulfonamides in the Treatment of Osteomyelitis and Pyogenic Arthritis, Bull. New York Acad. Med. **21**:87-98 (Feb.) 1945.

8. Buchman, J., and Blair, J. E.: Penicillin in the Treatment of Chronic Osteomyelitis, Arch. Surg. **51**:81-92 (Sept.) 1945.

9. Gerber, I. E.; Shwartzman, G., and Baehr, G.: Penetration of Penicillin into Foci of Infection, J. A. M. A. **130**:761-764 (March 23) 1946.

10. Heddaus, A.: Beiträge zur Heilserumbehandlung des Tetanus, München. med. Wchnschr. **61**:2186-2189 (Nov. 3) 1914.

11. Fiolle, J., and Fiolle, P.: Essais d'hématose artificielle et d'angéiothérapie artérielle, Marseille méd. **51**:597-603 (Sept. 1) 1914.

with the gas bacillus. Later, in this country, Hirsch and associates [12] safely and easily administered intracarotid injections of neoarsphenamine U. S. P. and sulfarsphenamine U. S. P. in the treatment of dementia paralytica. Kolmer [13] described the results of the introduction of various chemicals and serums into the carotid arteries of dogs with experimental pneumococcic and streptococcic meningitis. Later, he reported [14] cases of clinical meningitis in some of which recovery followed the intracarotid administration of serum and in some cases, Pregl's solution [15] and acriflavine. In 1933, Lamas [16] injected merbromin N. F. into the aorta in the treatment of subphrenic abscess. The 82 patients who received arterial injections included 5 with compound fracture, 8 with osteomyelitis and 50 with various abdominal conditions. With the intent of refining the technic of arterial injection, Huet and Bargeton [17] investigated the effects of various concentrations of different solutions on the vessel wall. They concluded that isotonicity is desirable and that the p_H should lie between 7.0 and 8.3, in order that spasm and organic changes might be avoided. In 1938, Luccarelli [18] published a series of 36 cases of infection of an extremity, with and without gangrene, and 1 case of meningitis, in all of which by the introduction of "salvakra" (a preparation of gentian violet medicinal) into the major artery supplying the part. Although it is difficult to estimate his success from the short case reports, his succinct introduction on the rationale of the method is excellent. In short, the ingenuity displayed in these reports is more impressive than the account of the therapeutic efficiency of the injected substances.

With the development of future antibiotics, the anticipated increase in range of action may possibly be accompanied with a greater toxicity.

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12. Hirsch, H. L.; Myerson, A., and Halloran, R. D.: Intracarotid Route in the Treatment of General Paresis, Boston M. & S. J. **192**:713-717 (April 9) 1925.

13. Kolmer, J. A.: The Intracarotid Treatment for Experimental Pneumococcus Meningitis, Arch. Otolaryng. **9**:509-527 (May) 1929.

14. Kolmer, J. A.: The Intracarotid Method of Treatment for Meningitis with Recoveries, J. A. M. A. **96**:1358-1361 (April 25) 1931.

15. Pregl's solution (concentrated) is a complex aqueous solution containing 3 per cent of available iodine in the form of hypoiodite and hypoiodate ions and some free iodine (Cowan, A., and Cowan, T. H.: Superficial Punctate Keratitis, Arch. Ophth. **19**:709-713 [May] 1938, p. 710).

16. Lamas, A. C.: Therapeutique par voie arterielle, Cong. franç. de chir. **42**:384-398, 1933.

17. Huet, P., and Bargeton, D.: Sur quelques effets des injections intra-artérielles, Presse méd. **44**:677-681 (April 22) 1936.

18. Luccarelli, V.: L'angioterapia arteriosa nella affezioni gravi degli arti, Policlinico (sez. prat.) **45**:1985 (Oct. 31) 1938.

In this connection, it may be noted that in 1909 von Oppel [19] compared the effects of injecting cocaine into the aorta and into the inferior vena cava of rabbits. He discovered that a given dose was eight to ten times as toxic in the vein as in the artery and concluded that the larger the capillary bed distal to the site of the injection, the lower the toxicity.

The technic of intra-arterial injection need not be confined to the administration of antibacterial substances. Other physiologically active substances and other antibiotic agents may be utilized in the same manner. As long ago as 1910, Ransohoff [20] induced regional anesthesia by injecting cocaine into peripheral arteries. It is our feeling that the method is fully worthy of more intensive investigation.

SUMMARY AND CONCLUSIONS

The rationale of the arterial administration of antiseptic substances is presented.

Levels of penicillin in bone marrow following single intramuscular, intravenous and intra-arterial injections were compared. With reference to these levels, no consistent difference with respect to bone marrow levels could be demonstrated between the intravenous and the intra-arterial route of administration.

An intra-arterial injection following a preliminary intravenous or intra-arterial dose resulted in a concentration of penicillin in the bone marrow far in excess of that obtained by a single injection of the same total dose.

The application of these observations to the treatment of infectious processes in bones is discussed.

Miss B. Toharsky and Miss R. Schapira gave technical assistance.

Fifth Avenue and One Hundredth Street.

19. von Oppel, W. A.: Experimentelle Grundlagen der arteriellen Anästhesie, München. med. Wchnschr. **56**:1772-1775 (Aug. 31) 1909.

20. Ransohoff, J. L.: Terminal Arterial Anaesthesia, Ann. Surg. **51**:453-456 (April) 1910.

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IN

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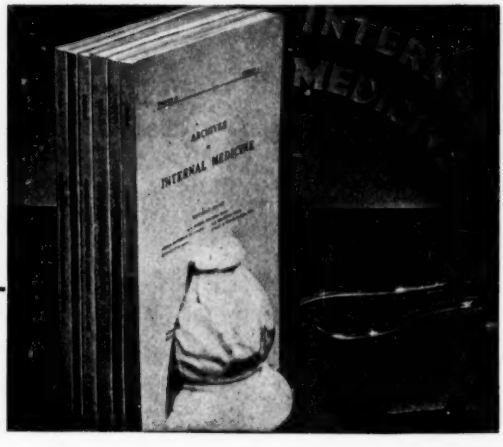

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